Dissertation on

"CLINICAL AND BIOCHEMICAL CORRELATION OF SKELETAL MYOPATHY IN HYOPOTHYROID PATIENTS"

Submitted in partial fulfillment for the Degree of

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BRANCH – I

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CERTIFICATE

This is to certify that the dissertation titled "**CLINICAL AND BIOCHEMICAL CORRELATION OF SKELETAL MYOPATHY IN HYOPOTHYROID PATIENTS"** is the bonafide original work done by **DR.DIVYA PRABHA G**, post graduate student, Institute of Internal medicine, Madras Medical College, Chennai-3, in partial fulfillment of the University rules and regulations for the award of MD Branch -1 General Medicine, under our guidance and supervision, during the academic year 2015-2018.

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I, **DR.DIVYA PRABHA .G** solemnly declare that dissertation titled **"CLINICAL AND BIOCHEMICAL CORRELATION OF SKELETAL MYOPATHY IN HYPOTHYROID PATIENTS"** is a bonafide work done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 during March 2017 to August 2017 under the guidance and supervision of my unit chief **Prof. S.USHA LAKSHMI M.D.,FMMC.,** Professor of Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University, towards partial fulfillment of requirement for the award of M.D. DEGREE IN GENERAL MEDICINE BRANCH-I.

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ABBEREVIATIONS

ANTI TPO	-	Anti thyroid peroxidase
fT4	-	Free thyroxine
AST	-	Aspartate transaminase
SGOT	-	Serum glutamyl oxaloacetate transferases
CK	-	Creatine kinase
LDH	-	Lactate dehydrogenase
LDL	-	Low density lipoprotein
CRP	-	C-reactive protein
CNS	-	Central nervous system
RBF	-	Renal blood flow
GFR	-	Glomerular filtration rate
CKD	-	Chronic kidney disease
SERM	-	Selective estrogen receptor modulators
PPI	-	Proton pump inhibitors
MI	-	Myocardial infarction
ATP	-	Adenosine tri phosphate
DTR	-	Deep tendon reflexes
TSH	-	Thyroid stimulating hormone
TFT	-	Thyroid function test
TKI	-	Tyrosine kinase inhibitors
$Al(OH)_3$	-	Aluminium hydroxide
CAD	-	Coronary artery disease
EMG	-	Electromyography

CONTENTS

INTRODUCTION

INTRODUCTION

Hypothyroidism is one of the most commonly occurring thyroid disorders worldwide. Muscle involvement in hypothyroidism is common with 30-80% of hypothyroid patients, presenting with muscular symptoms varying from myalgia to myopathy. This study is used to confirm the involvement of muscles in hypothyroidism using biochemical markers such as serum CK, LDH, AST and also to correlate the activity of these muscle enzymes with $T_{3,}T_{4,}$TSH levels.

The neuromuscular manifestations of hypothyroidism vary from delayed relaxation of DTR to full blown myopathy. Myopathies associated with hypothyroidism can be divided in to five subtypes: Kocher-debre-semelaigne syndrome, Hoffmann's syndrome, Atrophic form, Myasthenic syndrome with polymyositis like syndrome .These syndromes present as muscle stiffness, pseudohypertrophy, varying degrees of muscle weakness and painful muscle cramps.

The elevation of serum CK occurs in 70-90% of the patients with hypothyroidism and in thyroid myopathy, it will be very high; in some patients 10-100 times greater than the normal level with the help of this biochemical tests, we can identify the thyroid myopathy at the earliest and adjust the dose of L-thyroxine. Once the hormone replacement is initiated, most of the symptoms regress slowly with time.

Myopathy can be the only presenting feature of hypothyroidism even causing acute myoedema or bilateral foot drop. If a patient present with myopathic features hypothyroidism should be ruled out initially, as it is a reversible cause and has good prognosis.

AIMS AND OBJECTIVES

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To study the clinical and biochemical correlation of skeletal myopathy in hypothyroid patients.

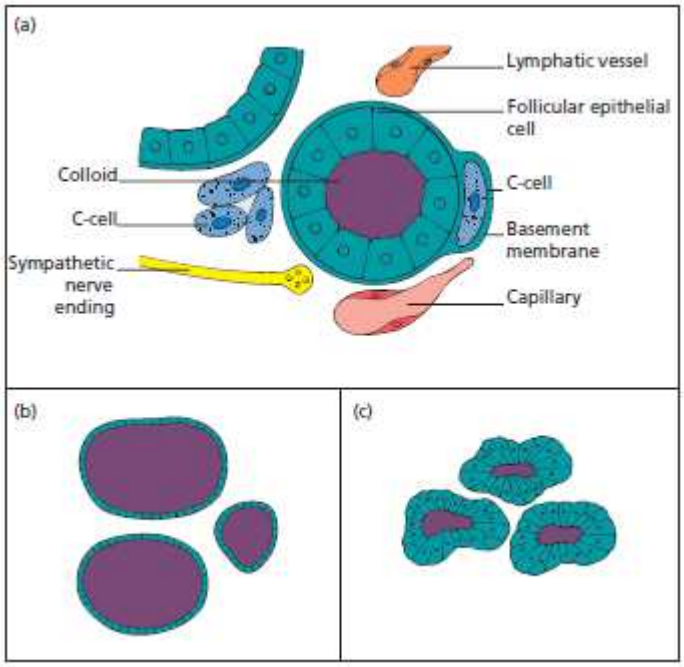
REVIEW OF LITERATURE

REVIEW OF LITERATURE

The thyroid is derived from greek word. (thyreos, shield plus eidos, form). It consists of two lobes connected by an isthumus, located anterior to the trachea between the cricoid cartilage and the suprasternal notch. The normal thyroid is 12-20g in size, highly vascular,and soft in consistency. The thyroid gland produces two hormones, thyroxine (T_4), triiodothyronine (T_3).

Four parathyroid glands, which produce parathyroid hormones are located posterior to each pole of the thyroid. Autoimmune destruction of the thyroid gland can cause over production of thyroid Hormones (THYROTOXICOSIS), or cause glandular destruction and hormone deficiency (HYPOTHYROIDISM).

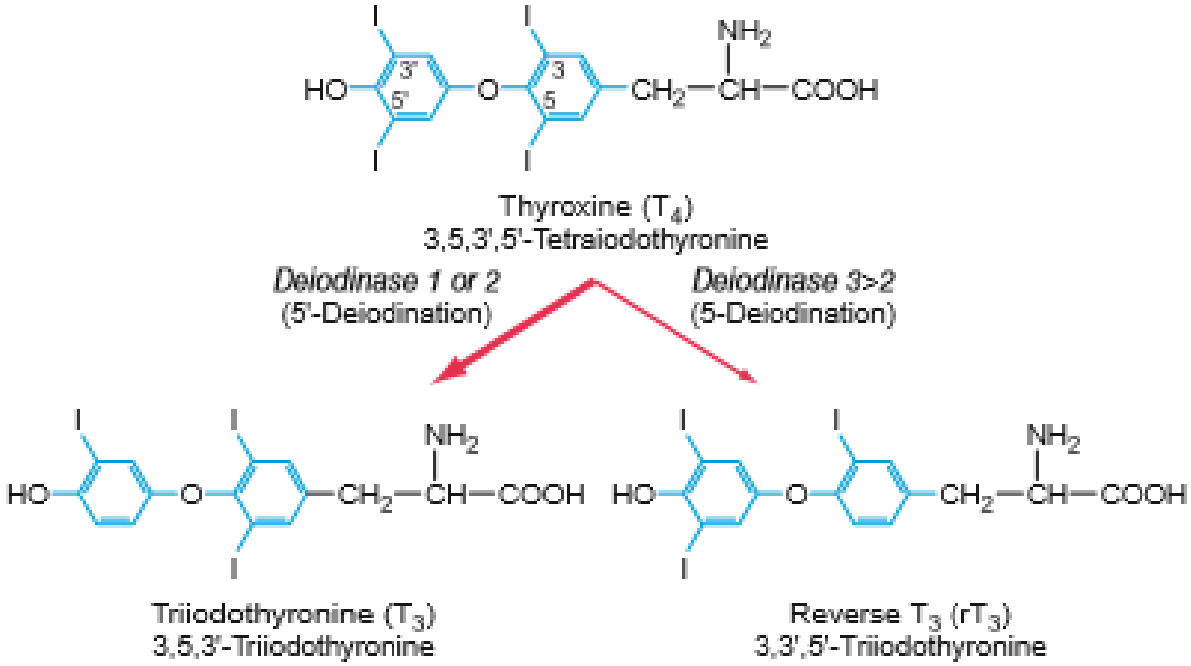
HISTOLOGY-THYROID GLAND:



a. Euthyroid follicles are shown lined with cuboidal epithelium and lumens filled with gelatinous colloid that contains stored thyroid hormone. Surrounding each follicle is a basement membrane enclosing parafollicular C-cells within stoma containing fenestrated capillaries, lymphatic vessels, sympathetic nerve endings.
b. Underactive follicles with flattened epithelial cells and increased colloid.
c. Overactive follicles with tall, columnar epithelial cells and reduced colloid.

REGULATION OF THYROID AXIS:

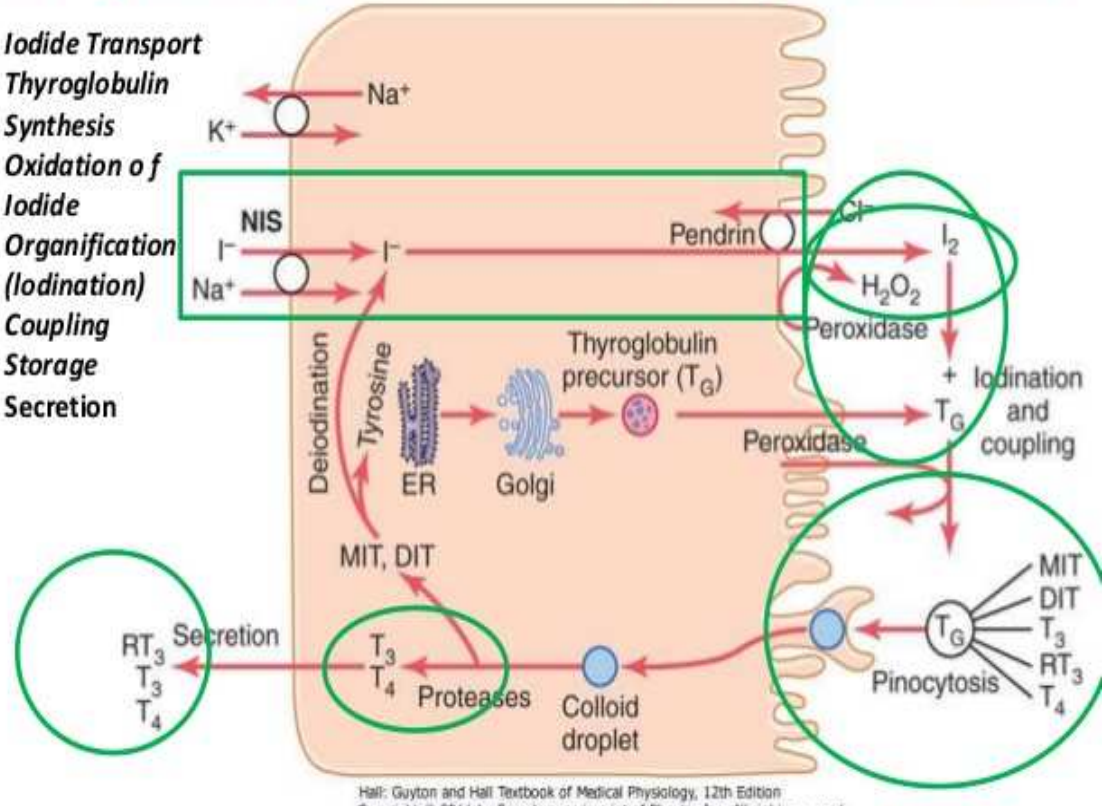
STUCTURES OF THYROID HORMONES:

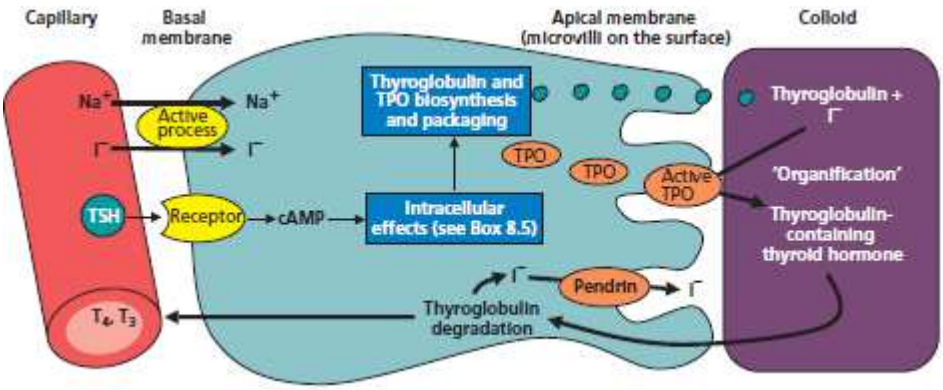


Thyroxine contains four iodine atoms. Deiodination leads to the potent hormone Triiodothyronine (T_3)or the inactive hormone reverse T_3

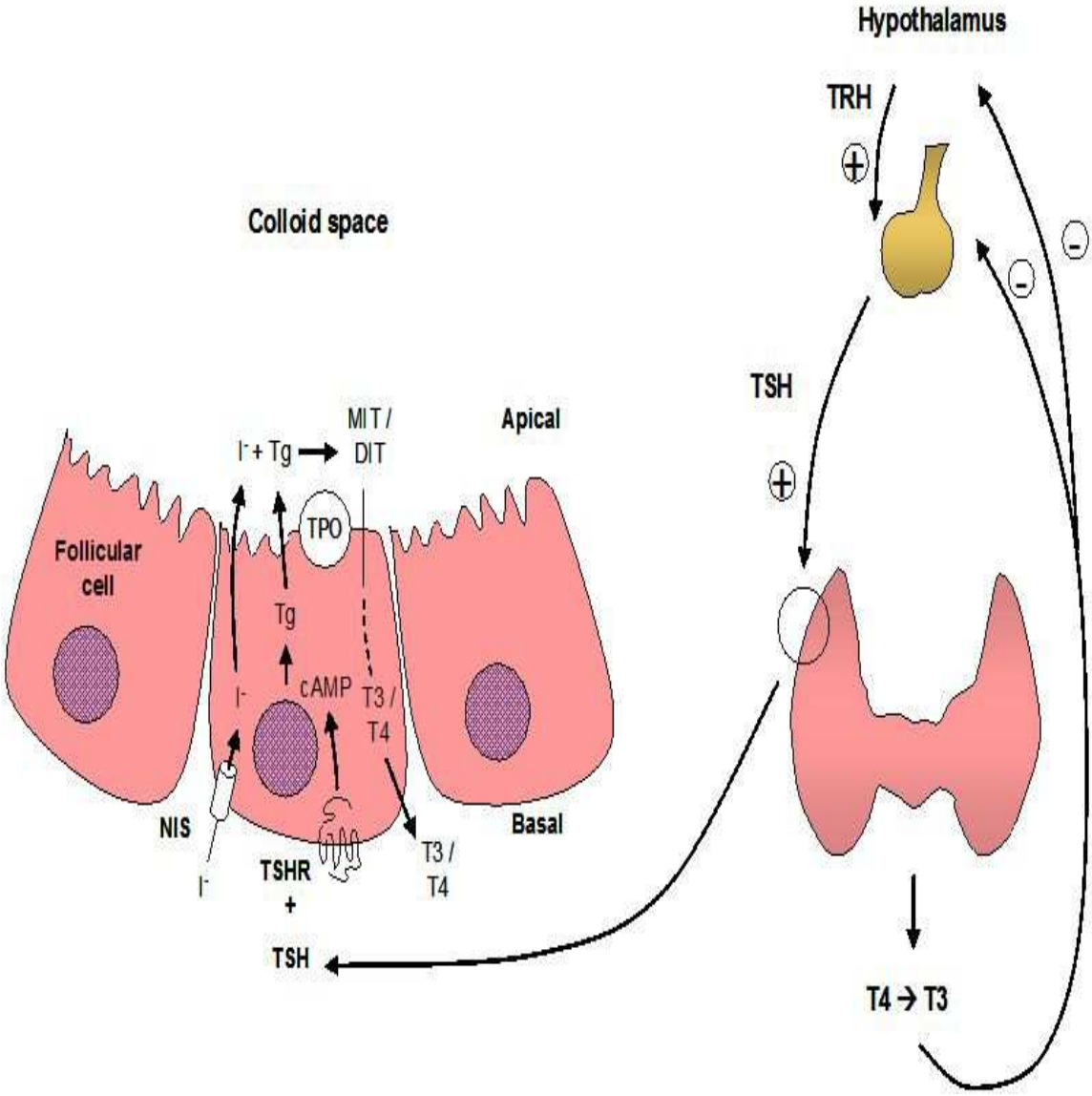
Bio-synthesis and Secretion of Thyroid Hormone

1. *Iodide Transport*
2. *Thyroglobulin Synthesis*
3. *Oxidation of Iodide*
4. *Organification (Iodination)*
5. *Coupling*
6. *Storage*
7. Secretion

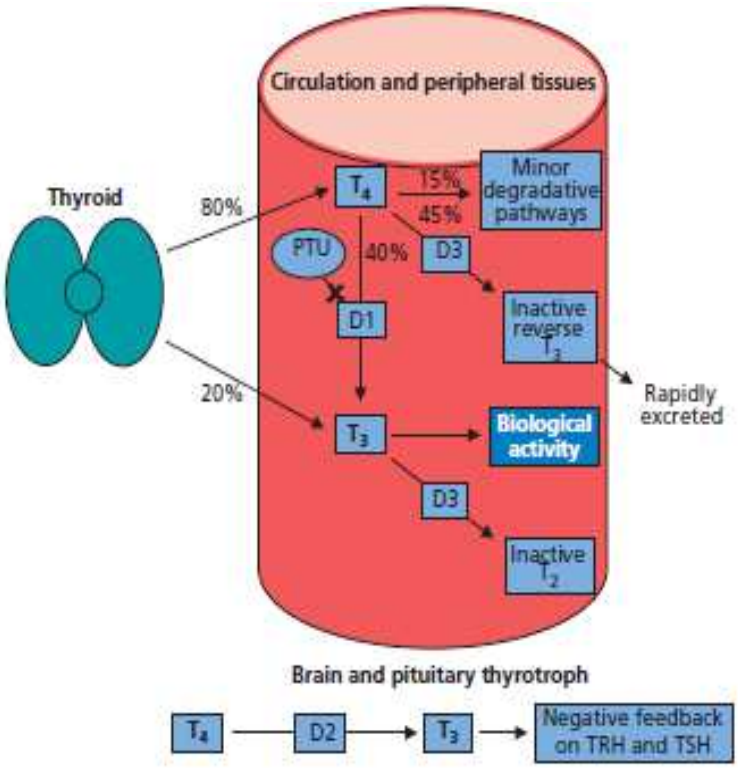




REGULATION OF THYROID HORMONE SYNTHESIS:



METABOLISM OF THYROID HORMONES IN THE CIRCULATION:



HYPOTHYROIDISM:

Hypothyroidism implies reduced production of thyroid hormone. Primary hypothyroidism refers to permanent loss or destruction of the thyroid through autoimmune destruction called as Hashimoto disease[1] or due to irradiation injury. Hypothyroidism is associated with compensatory thyroid enlargement.

Central or Secondary hypothyroidism occurs due to decreased stimulation of a normal gland is the result of hypothalamic or pituitary disease or defects in the TSH molecule.

In sub acute thyroiditis, transient or temporary hypothyroidism occurs.[2] 99% of cases of hypothyroidism are due to primary hypothyroidism. <1% of cases are due to TSH deficiency or other causes.

Clinical hypothyroisism can occur despite normal or increased thyroid hormone production due to reduced action of thyroid hormone at the tissue level.

Consumptive hypothyroidism occurs due to accelerated inactivation of thyroid hormone by the type 3 iodo-thyronine deiodinase[3]. Overt hypothyroidism, defined as an elevated serum TSH concentration and reduced free throxine concentration (fT4)[4].

Subclinical hypothyroidism is defined as an elevated serum TSH concentration with a normal serum fT4 levels [5]with few or no apparent clinical features of hypothyroidism.

The incidence of hypothyroidism is higher among women, in the elderly[6]. The risk of progression from subclinical to overt hypothyroidism is related to serum TSH elevation and the presence of anti TPO antibodies. Neonatal screening programs for congenital hypothyroidism identifies the disease in 1 in 3000 newborns[7].

CAUSES OF HYPOTHYROIDISM

Primary Hypothyroidism

Acquired
Hashimoto thyroiditis
Iodine deficiency (endemic goiter)
Drugs blocking synthesis or release of T_4 (e.g., lithium, ethionamide, sulfonamides, iodide)
Goitrogens in foodstuffs or as endemic substances or pollutants
Cytokines (interferon-α, interleukin 2)
Thyroid infiltration (amyloidosis, hemochromatosis, sarcoidosis, Riedel struma, cystinosis, scleroderma)
Postablative thyroiditis due to ^{131}I, surgery, or therapeutic irradiation for nonthyroidal malignancy

Congenital
Iodide transport or utilization defect (NIS or pendrin mutations)
Iodotyrosine dehalogenase deficiency
Organification disorders (TPO deficiency or dysfunction)
Defects in thyroglobulin synthesis or processing
Thyroid agenesis or dysplasia
TSH receptor* defects
Thyroidal G_s protein abnormalities (pseudohypoparathyroidism type 1a)
Idiopathic TSH unresponsiveness

Transient (Post-thyroiditis) Hypothyroidism

Following painless (including postpartum thyroiditis) or painful subacute thyroiditis

Consumptive Hypothyroidism

Rapid destruction of thyroid hormone due to D3 expression in large hemangiomas or hemangioendotheliomas

Defects of Thyroxine to Triiodothyronine Conversion

Selenocysteine insertion sequence–binding protein 2 (SECISBP-2) defect

Drug-Induced Thyroid Destruction

Tyrosine kinase inhibitor (sunitinib)

Central Hypothyroidism

Acquired
Pituitary origin (secondary)
Hypothalamic disorders (tertiary)
Bexarotene (retinoid X receptor agonist)
Dopamine or severe illness

Congenital
TSH deficiency or structural abnormality
TSH receptor defect

Resistance to Thyroid Hormone

Generalized
"Pituitary" dominant

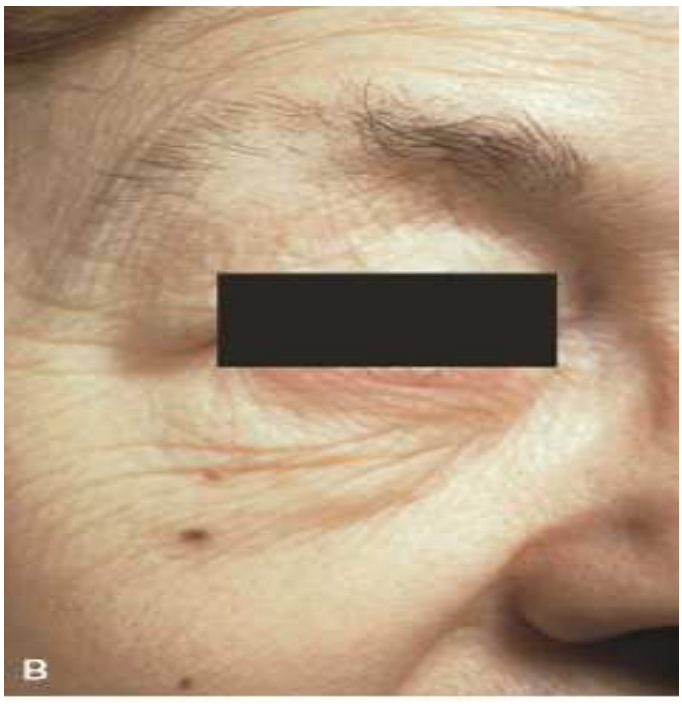
CLINICAL FEATURES-HYPOTHYROIDISM

Symptoms	Signs
Tiredness, weakness	Dry coarse skin; cool peripheral extremities
Dry skin	Puffy face, hands, and feet (myxedema)
Feeling cold	Diffuse alopecia
Hair loss	Bradycardia
Difficulty concentrating and poor memory	Peripheral edema
Constipation	Delayed tendon reflex relaxation
Weight gain with poor appetite	Carpal tunnel syndrome
Dyspnea	Serous cavity effusions
Hoarse voice	
Menorrhagia (later oligomenorrhea or amenorrhea)	
Paresthesia	
Impaired hearing	

SKIN AND APPENDAGES:

Accumulation of hyaluronic acid alters the ground substance in the dermis.[8]Hyaluronic acid is hygroscopic producing the mucinous edema which causes thickened features and puffy appearance.

Puffy eyes and thickened skin.



Loss of lateral aspect of the eyebrows present in this patient, known as Queen Anne's Sign.

Myxedematous tissue is characterized by boggy and non pitting edema around the eyes, on the dorsa of the hands & feet and in the supraclavicular fossae. It causes thickening of the pharyngeal & laryngeal mucous membranes & tongue enlargement. The secretions of the sweat glands and sebaceous glands are reduced, leading to dryness & coarseness of the skin.

Wounds heal slowly. Easy bruising occurs as the capillary fragility increases. Head and body hair is dry and brittle. Hair loss is seen in lateral aspect of eyebrows, but is not specific for hypothyroidism. Nails are brittle and grow slowly. Histopathologic examination of skin shows hyperkeratosis with plugging of hair follicles and sweat glands. In hashimoto thyroiditis, vitiligo occurs as a component of polyendocrine syndromes.

CARDIOVASCULAR SYSTEM:

Due to reduction in stroke volume & heart rate, cardiac output at rest is decreased. Peripheral vascular resistance at rest is increased. These changes leads to narrowing of pulse pressure, prolongation of circulation time and decreased blood flow to the tissues.[9] The reduction in cutaneous circulation is responsible for the coolness and pallor of the skin and the sensitivity to cold. In most tissues, decrease in blood flow is proportional to the decrease in oxygen consumption, so the arterio- venous difference

remains normal. The hemodynamic alterations at rest resemble those of congestive cardiac failure.

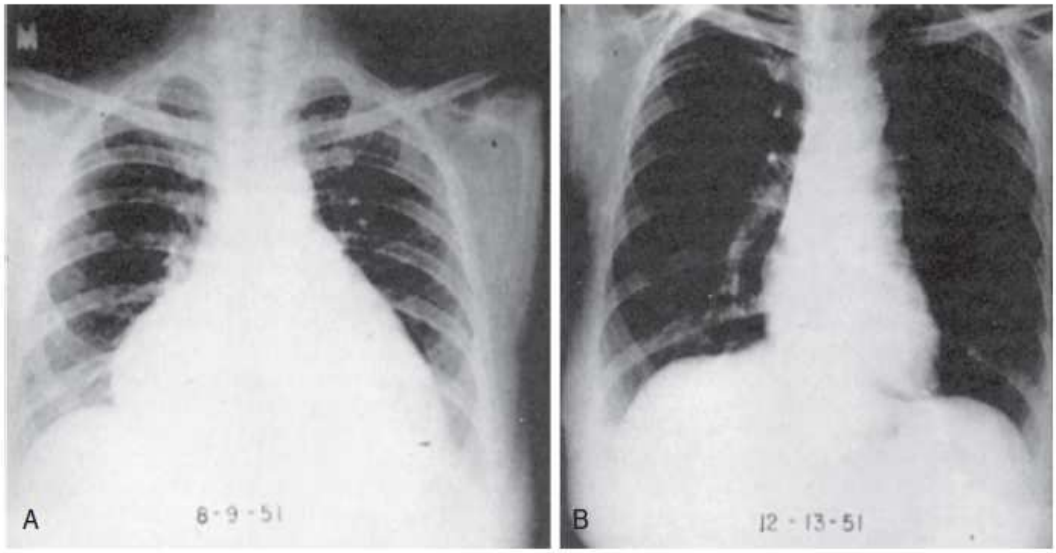
Cardiac silhouette is enlarged and heart sounds are decreased in intensity in severe primary hypothyroidism[10] due to pericardial effusion. Angina pectoris may first appear or worsen during treatment of the hypothyroid state with thyroid hormone, although most patients with hypothyroidism and coronary heart disease have no change, or improvement, in anginal symptoms with T_4 treatment.

Electrocardiographic changes include sinus bradycardia, prolongation of the PR interval, low amplitude of the P wave and QRS complex, alterations of the ST segment, and flattened or inverted T waves. Pericardial effusion is responsible for the low amplitude in severe hypothyroidism.

ECHO in overt hypothyroid patients show left ventricular diastolic dysfunction.

Levels of homocysteine, creatine kinase, aspartate amino transferase and lactate dehydrogenase may be increased in hypothyroidism.[12] Source of the enzymes is skeletal, not cardiac muscle. Sequential cardiac biopsies in a hypothyroid patient with heart failure showed that messenger RNA (mRNA) levels from genes regulated by thyroid hormone and important for the strength of myocardial contraction were normalized after T_4 treatment.

The combination of large heart, hemodynamic and electrocardiographic alterations and the serum enzyme changes has been termed myxedema heart. In the absence of coexisting organic heart disease, treatment with thyroid hormone corrects the hemodynamic, electrocardiographic and serum enzyme alterations of myxedema heart size to normal.



A-CXR in a patient with myxedema heart disease. The patient had signs of severe congestive heart failure and was given thyroid hormone alone.

B-Within 4 months, the heart had returned to normal size and there was no evidence of underlying heart disease.

Cardiovascular outcome studies suggest that improvement from treatment of hypothyroidism, especially subclinical hypothyroidism, is primarily in those who are middle age and not older individuals (older than 65 years of age).

Hypothyroidism associated with elevation of LDL cholesterol, serum triglcerides, & CRP improved with T_4 treatment.[13] Hypothyroidism is a risk factor for atherosclerosis and cardiovascular diseases.[14]

RESPIRATORY SYSTEM:

Breathing is affected due to an effect on central regulation of respiration as well as innervation and function of the respiratory muscles, upper airway and tongue.[15]Lung volumes are usually normal, but maximal breathing capacity and diffusion capacity are reduced. In severe hypothyroidism, myxedematous involvement of respiratory muscles and depression of both hypoxic and hypercapnic ventilatory drives may cause alveolar hypoventilation and carbon-di-oxide retention, which in contribute to the development of myxedema coma. Obstructive sleep apnoea in hypothyroid patients is reversed with restoration to euthyroid state.[16]

ALIMENTARY SYSTEM:

Most of the patients experience modest gain in weight, but appetite is usually reduced. The weight gain that occurs is caused partly by retention of fluid by the hydrophilic glycoprotein deposits in the tissues, but generally does not exceed 10% of body weight.

Peristaltic activity is decreased and decreased food intake leads to constipation. Fecal impaction leads to myxedema megacolon. Gaseous distension of abdomen leads to myxedema ileus.[17]

Elevations in the serum levels of carcino embryonic antigen, which may occur on the basis of hypothyroidism alone, add to the impression that an obstruction is present. Ascitic fluid rich in protein and glycosaminoglycans can occur in association with pleural and pericardial effusions.

Achlorhydria after maximal histamine stimulation may be present in patients with primary hypothyroidism. Circulating antibodies against gastric parietal cells have been found in one third of the patients with primary hypothyroidism and may be secondary to atrophy of the gastric mucosa. Hypothyroid patients with positive parietal cell antibodies have a higher T_4 requirement compared with antibody-negative patients.

The association of perinicious anaemia and other autoimmune diseases with the primary hypothyroidism reflects that autoimmunity play a important role in the pathogenesis of these diseases.[18]

Hypothyroid patients have a risk of developing cholelithiasis and nonalcoholic fatty liver disease.[19]

Hypothyroidism has complex effects on intestinal absorption. Although the rates of absorption for many substances are decreased, the total amount absorbed may be normal or even increased because the decreased bowel motility may allow more time for absorption.

Liver function tests are usually normal, but levels of transaminases may be elevated, probably because of impaired clearance. Atrophy of the gastric and intestinal mucosa and myxedematous infiltration of the bowel wall may be demonstrated on histologic examination. The colon may be greatly distended, and the volume of fluid in the peritoneal cavity is usually increased.

CENTRAL AND PERIPHERAL NERVOUS SYSTEM:

Thyroid hormone is essential for CNS development.[20]Deficiency in fetal life or at birth impairs neurological development, including hypoplasia of cortical neurons with poor development of cellular processes, retarded myelination, and reduced vascularity. If the deficiency is not corrected in early postnatal life, the damage is irreversible. Deficiency of thyroid hormone beginning in adult life causes less severe manifestations that usually respond to treatment with the hormone. Cerebral blood flow is reduced, but cerebral oxygen

consumption is usually normal. In severe cases, decreased cerebral blood flow leads to hypoxia.

Slowness of speech, memory disturbances, lethargy, somnolence and prominent dementia in elderly patients.[21]

Psychiatric disorders are of paranoid or depressive type, may cause agitation. (MYXEDEMA MADNESS).[22] Headaches are frequent. Cerebral hypoxia due to circulatory alterations may predispose to confusional attacks and syncope, which may be prolonged and lead to stupor or coma. Other factors predisposing to coma in hypothyroidism are sever cold, infection, trauma, hypoventilation with CO_2 retention and depressant drugs.

Epileptic seizures have been reported and tend to occur in myxedema coma. Night blindness is due to deficient synthesis of the pigment required for dark adaptation. Hearing loss of the perceptive type is frequent due to myxedema of the eighth cranial nerve and serous otitis media.

Thick, slurred speech and hoarseness are due to myxedematous infiltration of the tongue and larynx respectively. Body movements are slow and clumpsy, cerebellar ataxia can occur. Numbness & tingling sensation of fingers are common due to compression by glycosaminoglycan deposits in and around the median nerve in the carpal tunnel. (CARPAL TUNNEL SYNDROME).[23]

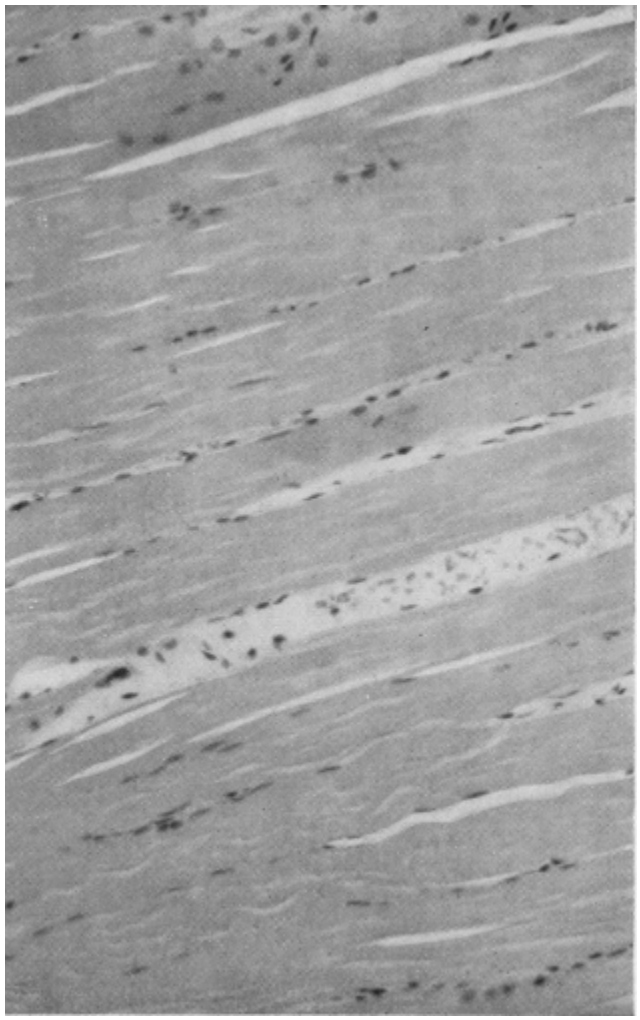
There is an association of Alzheimer disease and hypothyroidism.[24] There is an increase in cerebrospinal fluid reverse T_3 levels in Alzheimer disease patients, all with normal circulating thyroid hormone levels, suggesting the potential for altered thyroid hormone metabolism in the brain. A corticosteroid -responsive encephalopathy is associated with chronic hashimoto thyroiditis but may be linked to autoimmunity rather than a process mediated specifically by low thyroid hormone levels or thyroid autoantibodies.

Histopathological examination of the brain in patients with untreated hypothyroidism reveals that the nervous system is edematous with mucinous deposits in and around nerve fibres. In patients with cerebellar ataxia, neural myxedematous infiltrates of glycogen and mucinous material are present in the cerebellum.

MUSCULAR SYSTEM:

Stiffness and aching of muscles are common in hypothyroidism. Tendon reflexes are slow during the relaxation phase, producing “HUNG UP REFLEXES” due to decrease in the rate of muscle contraction and relaxation.[25] Muscle mass may be reduced or increased due to interstitial myxedema. Rarely, profound increase in muscle mass with slowness of muscular activity occurs in kocher – Debre - semelaigne or Hoffmann syndrome.

EMG–Normal/disordered discharge, hyperirritability / polyphasic action potentials. Muscle Biopsy-muscles are pale and swollen. Loss of normal striations in muscle fibres and separation by mucinous deposits. Type 1 muscle fibres predominate.



Muscle biopsy shows mild variation in fibre size; mild proliferation of sarcolemmal nuclei; few fibres shows central nuclei.

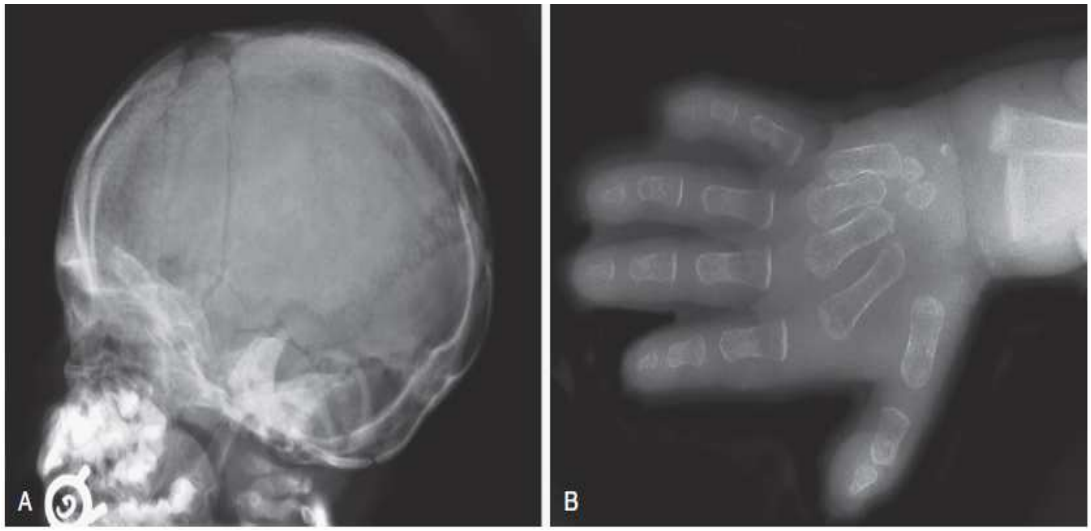
SKELETAL SYSTEM:CALCIUM AND PHOSPHOROUS METABOLISM:

Thyroid hormone is needed for normal growth and maturation of the skeleton.[26] Growth failure is due to a reduction in both protein synthesis and growth hormone especially of insulin like growth factor 1.

The thyroid hormone receptor isoforms alpha and beta have specific roles in bone maturation. Before puberty, thyroid hormone plays a major role in the maturation of bone.

Deficiency of thyroid hormone in early life leads to both a delay in development and an abnormal, stippled appearance of the epiphyseal centers of ossification (EPIPHYSEAL DYSGENESIS).Impairment in linear growth leads to dwarfism in which the limbs are disproportionately short in relation to the trunk but cartilage growth is unaffected. Children with prolonged hypothyroidism, even after adequate treatment, do not reach predicted height based on midparental height calculations.

Urinary excretion of calcium is decreased, as is the glomerular filtration rate, whereas fecal excretion of calcium and both urinary and fecal excretion of phosphorous is variable. The exchangeable pool of calcium and its rate of turnover are reduced, reflecting decreased bone formation and resorption.



A-X-ray skull of a 17 year old child patient shows posterior and anterior fontanels are open and sutures are not closed. The deciduous and permanent teeth are present.

B-X-ray of wrist shows delayed appearance of epiphyseal centers of the bones of the hand and the absence of the distal radial epiphysis.

RENAL FUNCTION:

Reversible decrease in RBF, GFR, tubular reabsorptive and secretory maxima are seen in hypothyroidism. Blood urea nitrogen and serum creatinine are normal, but uricacid levels may be increased.

The delay in water excretion appears to be due to decreased volume delivery to the distal diluting segment of the nephron as a result of the diminished renal perfusion. The impaired renal excretion of water and retention of water by the hydrophilic deposits in the tissues result in an increase in total body water, even though plasma volume is reduced.

This is the reason for occasional hyponatremia in hypothyroidism. Serum potassium levels remains normal. Serum magnesium levels are increased.

Increased prevalence of hypothyroidism in seen in CKD patients. Improvement in renal function has been demonstrated with T_4treatment.

HEMATOPOIETIC SYSTEM:

Vit B 12 and folate deficiency may occur. Higher incidence of pernicious anaemia occurs. Overt and subclinical hypothyroidism is present in 12% & 15% of patients with pernicious anaemia. TC-Normal, Platelet-Normal, decreased VIII, IX factors and increase in capillary fragility & decrease in platelet adhesiveness may lead to bleeding tendencies.[27]

REPRODUCTIVE FUNCTION:

Thyroid hormone influence sexual and reproductive function in both the sexes.[28] Infantile hypothyroidism, if untreated, leads to sexual immaturity, and juvenile hypothyroidism causes a delay in the onset of puberty followed by anovulatory cycles. Paradoxically, primary hypothyroidism may also rarely cause precocious sexual development and galactorrhoea presumably due to “spill over” of elevated TSH stimulating the luteinizing hormone(LH) receptor and elevated TRH initiating excess prolactin release.

Fertility is reduced and there is risk of spontaneous abortion and preterm delivery. Primary ovarian failure is seen in patients with hashimoto thyroiditis as a part of an autoimmune polyendocrine syndrome.

Hypothyroidism in men may cause decreased libido, erectile dysfunction and oligospermia. The metabolism of both androgens and oestrogens is altered in hypothyroidism. The sex hormone -binding globulin in plasma is decreased. The alterations in steroid metabolism are corrected by restoration of euthyroid state.

PITUITARY AND ADRENOCORTICAL FUNCTION:

In long-standing primary hypothyroidism, hyperplasia of the thyrotropes may cause the pituitary gland to be enlarged. This feature can be detected radiologically as an increase in the volume of the pituitary fossa. Rarely, the pituitary enlargement compromises the function of other pituitary cells and causes pituitary insuffiency or visual field defects.

Patients with severe hypothyroidism may be increased serum prolactin levels, stimulated by the elevation in thyrotrophin releasing hormone and proportional to the level of serum TSH elevation and galactorrhoea may develop in some patients. Treatment with thyroid hormone normalizes the serum prolactin and TSH levels and causes disappearance of galactorrhoea, if present.

Growth hormone is not directly regulated by thyroid hormone in humans, but thyroid hormone in humans, but thyroid status influences the growth hormone axis. Hypothyroid children have delayed growth and the response of growth hormone to provocative stimuli may be subnormal.

In severe, long-standing primary hypothyroidism, pituitary and adrenal function may be secondarily decreased, and adrenal insufficiency may be precipitated by stress or rapid replacement therapy with thyroid hormone, the rate of turnover of aldosterone is decreased, but the plasma level is normal.

Plasma renin activity is decreased, and sensitivity to angiotensin II is increased, which may contribute to the association of hypertension with hypothyroidism.

CATECHOLAMINES:

The plasma cyclic adenosine monophosphate (cAMP) response to epinephrine is decreased in hypothyroidism, suggesting a state of decreased adrenergic responsiveness. The fact that the responses of plasma cAMP to glucagon and parathyroid hormone are also decreased suggests that thyroid hormone have a general modulating influence on cAMP generation. The reduced adrenergic responsiveness associated with hypothyroidism has been linked to all steps to catecholamine signaling, including receptor and postreceptor actions, resulting in impaired cAMP response.

ENERGY METABOLISM : PROTEIN,CARBOHYDRATE AND LIPID METABOLISM:

The decrease in energy metabolism and heat production is reflected as a low basal metabolic rate, decreased appetite, cold intolerance and slightly low basal body temperature. Permeability of capillaries to protein is increased accounting for high level of protein in effusions and in cerebrospinal fluid.

Hypothyroidism is associated with reduction in glucose disposal to skeletal muscle and adipose tissue. Thyroid hormone has been stimulate expression of the insulin-sensitive glucose transporter (GLUT4), and the levels of this transporter are reduced in hypothyroidism. Hypothyroidism is also, however, associated with reduced gluconeo genesis.

Thyroid hormone down regulates expression of prohormone processing enzymes, which, therefore, have increased activity in hypothyroidism. Degradation of insulin, therefore, is slowed and the sensitivity to exogenous insulin may be increased. In a patient with preexisting diabetes mellitus who develops hypothyroidism, insulin requirements may be reduced.

Both the synthesis and the degradation of lipid are depressed in hypothyroidism. The decrease in the lipid degradation may reflect the decrease in post heparin lipolytic activity, as well as reduced LDL

receptors. Plasma free fatty acids in response to fasting, catecholamines, and growth hormone is impaired.

Impaired lipolysis of white fat in hypothyroid patients at baseline and in response to catecholamines reflects impaired free fatty acid mobilization. All of these abnormalities are relieved by treatment.

The role of adipocytokines, such as leptin, adiponectin, and resistin, in metabolic regulation has been increasingly recognized as well as the potential for interaction with thyroid hormone.

AUTOIMMUNE HYPOTHYROIDISM:

Autoimmunity is responsible for over 90% of noniatrogenic hypothyroidism in countries with iodine deficiency. The annual incidence of autoimmune hypothyroidism is around 80 per 100,000 men and 350 per 100,000 women.

All ages may be affected, although the average age of onset is between 40 and 60 years old. Juvenile and adolescent thyroiditis is the commonest cause of goiter in iodine-sufficient regions; atophic thyroiditis (primary myxedema) presents as hypothyroidism without a goiter.

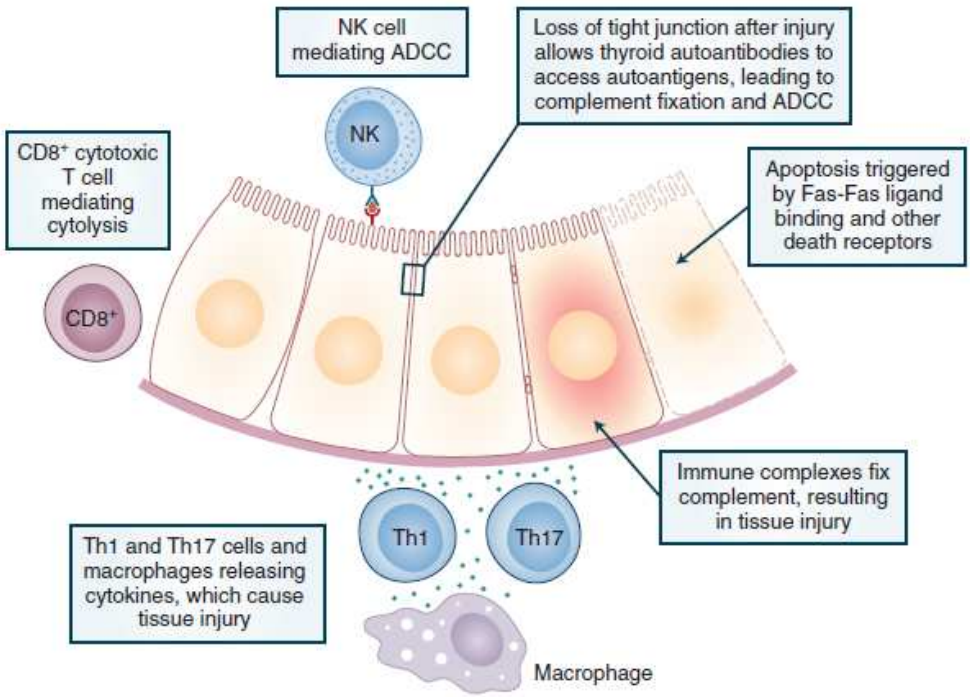
Circulating auto antibodies against thyroglobulin and TPO are present in almost all patients with autoimmune hypothyroidism. Up to 20% of patients with autoimmune hypothyroidism have TSH receptor antibodies that block the receptor, rather than stimulating it, as in graves

disease; in rare patients there may be switching from one type of antibody to the other, resulting in alternating hypothyroidism and hyperthyroidism.

Autoimmune hypothyroidism is commonly found in association with a range of autoimmune disorders, including pernicious anemia, systemic lupus erythematosus, Addison disease, celiac disease, and vitiligo.

A steroid responsive encephalopathy (Hashimoto encephalopathy) has been reported in individuals with positive TPO antibodies, irrespective of thyroid dysfunction.

PATHOGENESIS:



HISTOPATHOLOGY:

The pathologic features of autoimmune hypothyroidism vary from mild focal thyroiditis to extensive lymphocytic infiltration and fibrosis. In classical Hashimoto thyroiditis (STRUMA LYMPHOMATOSA), the thyroid gland may be diffusely enlarged or nodular; the tissue is pale and firm and has a rubbery texture. Typically, there is a diffuse lymphocytic infiltration with germinal center formation and obliteration of thyroid follicles, accompanied by a variable degree of fibrosis.

RISK FACTORS:

- GENETIC SUSCEPTIBILITY:

  The importance of genetic factors in the cause of autoimmune hypothyroidism is indicated by the frequent presence of thyroid auto antibodies, thyroid disease, and other autoimmune disorders in family members .Human leukocyte antigen (HLA)-D region polymorphisms play a role in susceptibility, and Hashimoto thyroiditis is associated with HLA-DR3 and to a lesser extent HLA-DR4. Polymorphisms are seen in the CTLA4 gene and in the MAG13 gene.

- NONGENETIC RISK FACTORS:

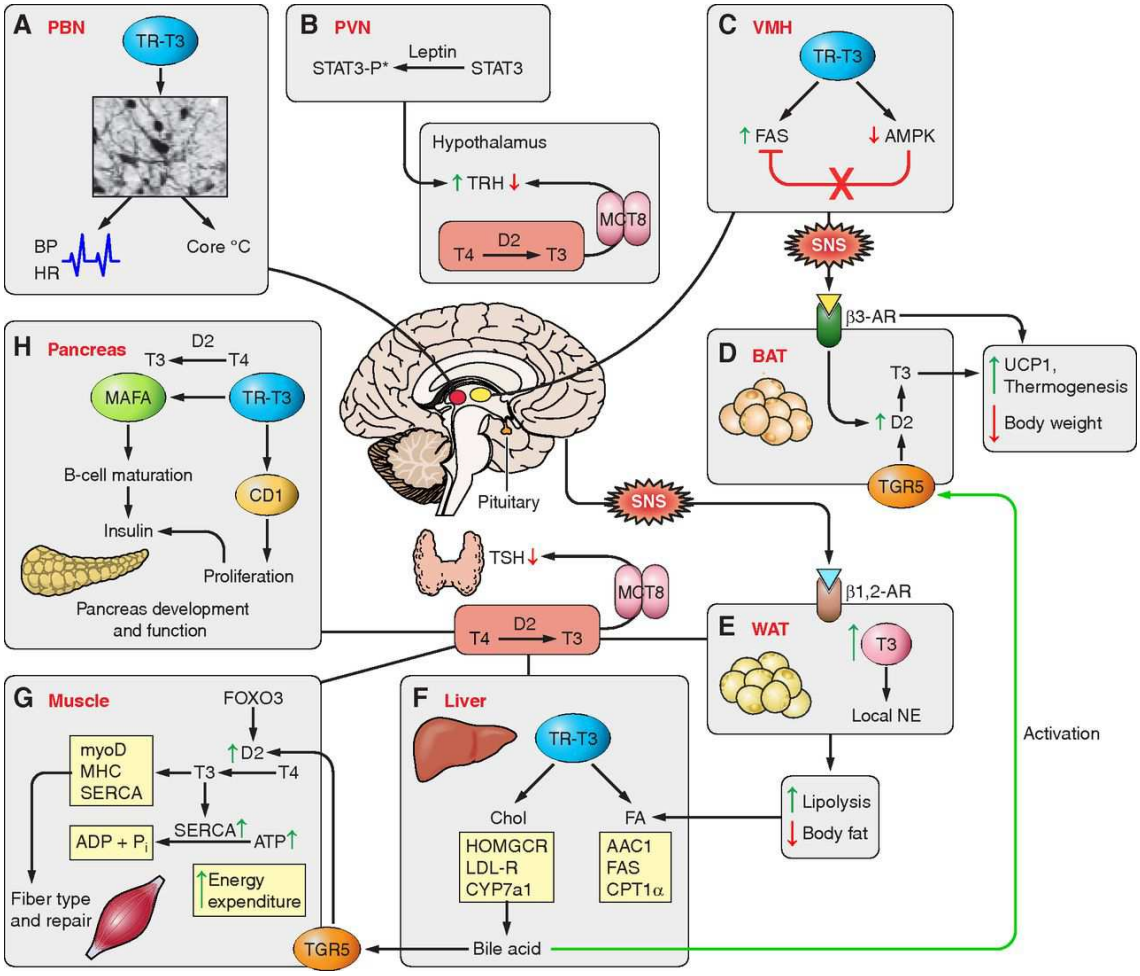
1. Sex and pregnancy.
2. Iodine and selenium.
3. Drugs –tyrosine kinase inhibitors (TKIs),lithium.
4. Smoking.
5. Irradiation.
6. Age.
7. Infection.

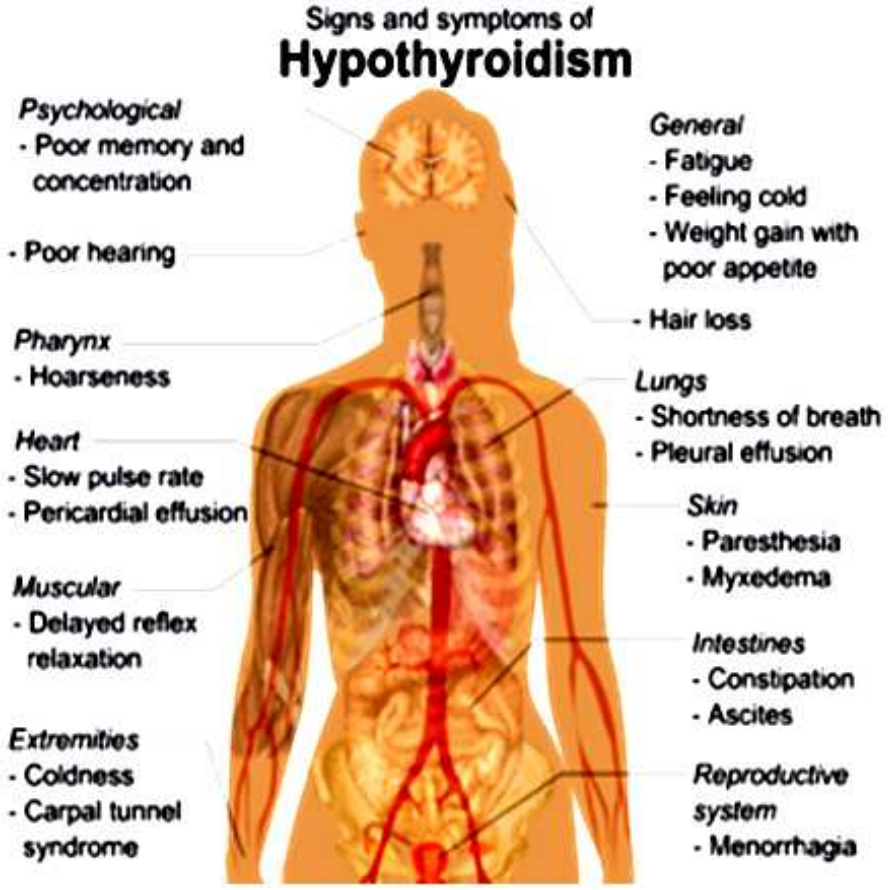
CLINICAL PICTURE:

Goiter, the hallmark of classic hashimoto disease, usually develops gradually and may be found during routine examination or by ultrasonography. When accompanied by pain and tenderness, it mimics painful subacute thyroiditis. The goiter is generally painless, moderate in size, and firm in consistency and moves freely on swallowing. The surface can be either smooth or nodular. Both lobes are enlarged, but the gland may be asymmetric.

The pyramidal lobe may also be enlarged, and rarely, adjacent structures, such as the trachea, esophagus, and recurrent laryngeal nerves, may be compressed.

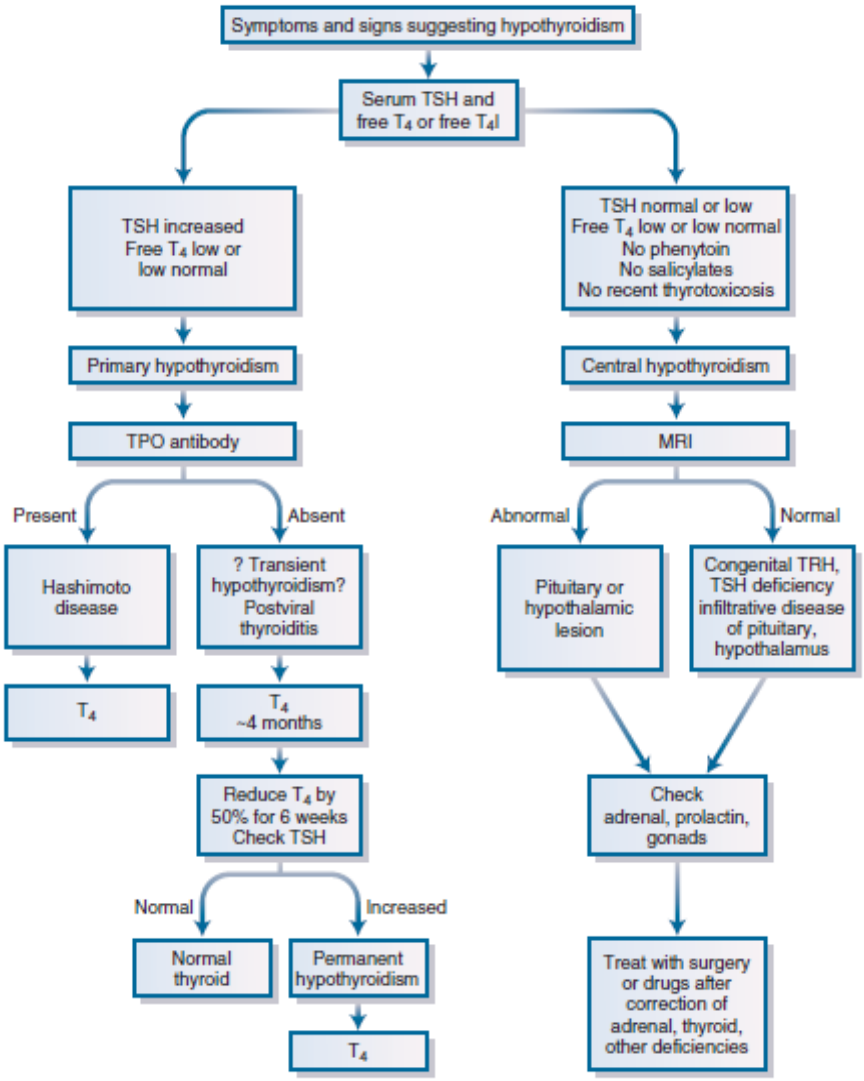
THYROID HORMONE EFFECT ON VARIOUS ORGANS:





a-Large tongue
b-coarse dry skin.

EVALUATION OF HYPOTHYROIDISM:



LABOROTARY EVALUATION OF PATIENTS WITH SUSPECTED HYPOTHYROIDISM OR THYROID ENLARGEMENT

TSH, Free T_4	TPO-Ab	Diagnosis
		TSH > 10 mU/L
Low	+	Primary hypothyroidism due to autoimmune thyroid disease
Low normal	+	Primary "subclinical" hypothyroidism (autoimmune)
Low or low normal	–	Recovery from systemic illness External irradiation, drug-induced, congenital hypothyroidism Iodine deficiency Seronegative autoimmune thyroid disease Rare thyroid disorders (amyloidosis, sarcoidosis, etc.) Recovery from subacute granulomatous thyroiditis
Normal	+, –	Consider TSH or T_4 assay artifacts
Elevated	–	Thyroid hormone resistance Blockade of T_4 to T_3 conversion (amiodarone) or a congenital 5′-deiodinase deficiency Consider assay artifacts
		TSH 5-10 mU/L
Low, low normal	+	Early primary autoimmune hypothyroidism
Low, low normal	–	Milder forms of nonautoimmune hypothyroidism (see earlier) Central hypothyroidism with impaired TSH bioactivity
Elevated	– (+)	Consider thyroid hormone resistance T_4 to T_3 conversion blockade (e.g., amiodarone)
		TSH 0.5-5 mU/L
Low, low normal	– (+)	Central hypothyroidism Salicylate or phenytoin therapy Desiccated thyroid or T_3 replacement
		TSH < 0.5 μU/L
Low, low normal	– (+)	"Post-hyperthyroid" hypothyroidism (^{131}I or surgery) Central hypothyroidism T_3 or desiccated thyroid excess Following excess levothyroxine withdrawal

TREATMENT:

CLINICAL HYPOTYRIDISM:

- If no residual thyroid function ,Daily replacement → Eltroxin - 1.6 microgram/Kg.BW(100-150 microgm),atleast 30 min before breakfast.
- In patients developing hypothyroidism after the treatment of grave' disease, lower replacement doses are sufficient. (75-125micro gm/day).
- Patients < 60 years without heart disease may be given 50-100microgram of levothyroxine daily.
- TSH responses are slow and should be seen after 2 months of initiating the treatment. clinical response of L-thyroxine replacement is also slow.
- Patient will have complete relief from symptoms after 3-6 months of achieving normal TSH levels.
- Increment or decrement of L-thyroxine is made in 12.5/25 microgm.
- T_4 overtreatment have an increased risk of AF and decreased bone density
- T_4 has $t_{1/2}$-7 days, if a dose is missed two doses can be at once.
- Increase in L-thyroxine requirements include malabsorption, SERM therapy, ingestion with a meal.

- Drugs interfering are $FeSO_4$, PPI, lovastatin, $Al(OH)_3$, rifampicin, Cholestyramine, calcium, amiodarone, TKI, carbamazepine, phenytoin.

Conditions That Alter Levothyroxine Requirements

Increased Levothyroxine Requirements

Pregnancy
Gastrointestinal Disorders
Mucosal diseases of the small bowel (e.g., sprue)
After jejunoileal bypass and small bowel resection
Impaired gastric acid secretion (e.g., atrophic gastritis)
Diabetic diarrhea

Therapy with Certain Pharmacologic Agents
Drugs That Interfere with Levothyroxine Absorption
Cholestyramine
Sucralfate
Aluminum hydroxide
Calcium carbonate
Ferrous sulfate

Drugs That Increase the Cytochrome P450 Enzyme (CYP3A4)
Rifampin
Carbamazepine
Estrogen
Phenytoin
Sertraline
? Statins

Drugs That Block T_4 to T_3 Conversion
Amiodarone

Conditions That May Block Deiodinase Synthesis
Selenium deficiency
Cirrhosis

Decreased Levothyroxine Requirements

Aging (65 years and older)
Androgen therapy in women

SUBCLINICAL HYPOTHYROIDISM:

If a women is pregnant/wants to conceive

When TSH>10mIU/L ,L - thyroxine is recommended,

If, TSH<10mIU/L,L- thyroxine is given

I. when pt is symptomatic,

II. positive TPO antibodies,

III. evidence of heart disease, and

IV. sustained elevation of TSH for more than 3 months.

Treatment started with low doses of L-thyroxine (25-50microgm/day).

PREGNANCY:

As maternal hypothyroidism leads to preterm delivery &adverse neurological outcomes in fetus, women should be euthyroid prior to conception and during early pregnancy. In presence of thyroid auto antibodies, even in euthyroid patients, miscarriage & preterm delivery can occur.

TFT should be done every 4 weeks up to 20 weeks, thereafter once in 6-8 weeks depending on L-thyroxine dose adjustment. L-thyroxine dose is increased up to 50% in pregnancy achieving TSH<2.5mIU/Lin first trimester, <3.0mIU/L during second and third trimester. Vitamin and iron supplements and L-thyroxine should be taken 4 hours apart.

ELDERLY PATIENTS:

Requirement is 20% less than younger patients. In CAD patients with hypothyroidism, 12.5-25 microgram/day should be initiated.

MYXEDEMA COMA:

L-thyroxine is given as single iv bolus of 500 microgram, continued as 50-100microgram/day. If iv preparation is not available, 500microgram of oral L-thyroxine is given by nasogastric tube. Alternatively 1)T_3 is given iv/thro NG tube in doses, 10-25microgram every 8-12 hours.2) combine L-thyroxine (200microgram) and T_3 (25microgram) as a single iv bolus followed by L-thyroxine (50-100 microgram), T_3liothyronine (10 microgram) every 8 th hourly.

Supportive therapy to correct metabolic disturbances .As there is impaired adrenal reserve, parenteral hydrocortisone (50mg/6thhrly) should be given. External warming done if temperature <30 degree Celsius. Space blankets are used to prevent heat loss.

MYOPATHY IN HYPOTHYROIDISM:

Hypothyroid patients will have myopathy rather than functional muscle disease. Serum muscle enzymes will be elevated in these conditions. Ebashi.et.al used serum creatine kinase as a diagnostic aid in progressive muscular dystrophy in 1959 [29]. Since then, it is an important marker for muscle damage. Age, race, lean body mass and physical activity determines the serum CK levels in healthy individuals.[30]

57-90% of patients with hypothyroidism have elevation of serum CK[31].CK-MB, isoform of CK, marker for diagnosis of MI. It is also increased in various inflammatory conditions of skeletal muscles. Even without apparent myocardial damage in hypothyroid patients, CK and troponin levels are increased[32].

Skeletal muscle is affected profoundly in overt hypothyroidism when compared to subclinical hypothyroidism.[33] Prakash.A et.al study showed elevation of CK in 60% of hypothyroid patients (mostly CK-MM isoform) [34] & also increase in LDH & SGOT. Fleisher GA. et.al reported to have elevated LDH in hypothyroid patients.[35]

Griffith PD showed elevation of AST/SGOT in 60% of patients with hypothyroidism.[36] Enzyme activity of these muscle enzymes depends on the degree of hypothyroidism.[37,38.39,40,41.]

Histologically, muscle fibres shows enlargement, focal myofibrillar degeneration, glycogen accumulation, increase in central nuclei, mitochondrial aggregations and type II fibre atrophy.[42]

Myopathy caused by shift in distribution of muscle fibres from fast twitch fibres to slow twitch fibres.[43]In hypothyroidism reduction in glycolysis and oxidative phosphorylation leads to decreased ATP. Alteration in sarcolemmal membrane leads to increased cell permeability which further leads to leakage of enzymes from the cells.[44]

Due to raised turnover of enzymes also, serum enzyme activities are increased in hypothyroidism.[45]The common symptoms of myopathy in hypothyroidism includes proximal muscle weakness, muscle cramps, myoedema on percussion, delay in DTR,& rarely muscle hypertrophy. Severity of myopathy depends on the duration of thyroid hormone deficiency.

PERCUSSION MYOTONIA

PATIENT WITH CALF HYPERTROPHY

Hoffmann's syndrome, a form of hypothyroid myopathy, causes proximal muscle weakness and hypertrophy of muscles. Common muscle groups involved are the tongue, arm, leg muscles. Muscle hypertrophy and weakness resolve following treatment with thyroid hormone.

MATERIALS AND METHODS

MATERIALS AND METHODS

SETTING

This study was conducted at the Institute of Internal Medicine, Rajiv Gandhi Government General Hospital (RGGGH), Madras Medical College, Chennai.

ETHICS COMMITTEE APPROVAL

Obtained

STUDY DURATION

This study was conducted over a period of six months

(March 2017 - August 2017).

STUDY POPULATION

Patients with hypothyroidism admitted in medical wards and attending endocrine OP at the Institute of Internal Medicine.

SAMPLE SIZE

50 Patients

TYPE OF STUDY

Observational prospective study

INCLUSION CRITERIA

Patients with hypothyroidism admitted in medical ward and those attending Endocrine OP.

EXCLUSION CRITERIA

- Patients with acute onset of chest pain.
- Patients with dematomyositis or polymyositis.
- Patients with stroke or convulsions.
- Patients with muscular dystrophies.
- Delirium tremens.
- Rhabdomyolysis.
- Malignant hyperthermia.

DATA COLLECTION AND METHODS

On patients who have been admitted in medical wards and those attending endocrine OP, RGGGH, Chennai, an observational study on hypothyroidism patients for a period of 6 months (March 2017 – August 2017) . Patients selected for clinical study as per inclusion and exclusion criteria. Detailed history taking and clinical examination will be done. Serum levels of CK, LDH, SGOT, fT_3, fT_4, TSH, Urine Mb, USG-Neck will be estimated and in patients who have given consent, EMG and Muscle biopsy done.

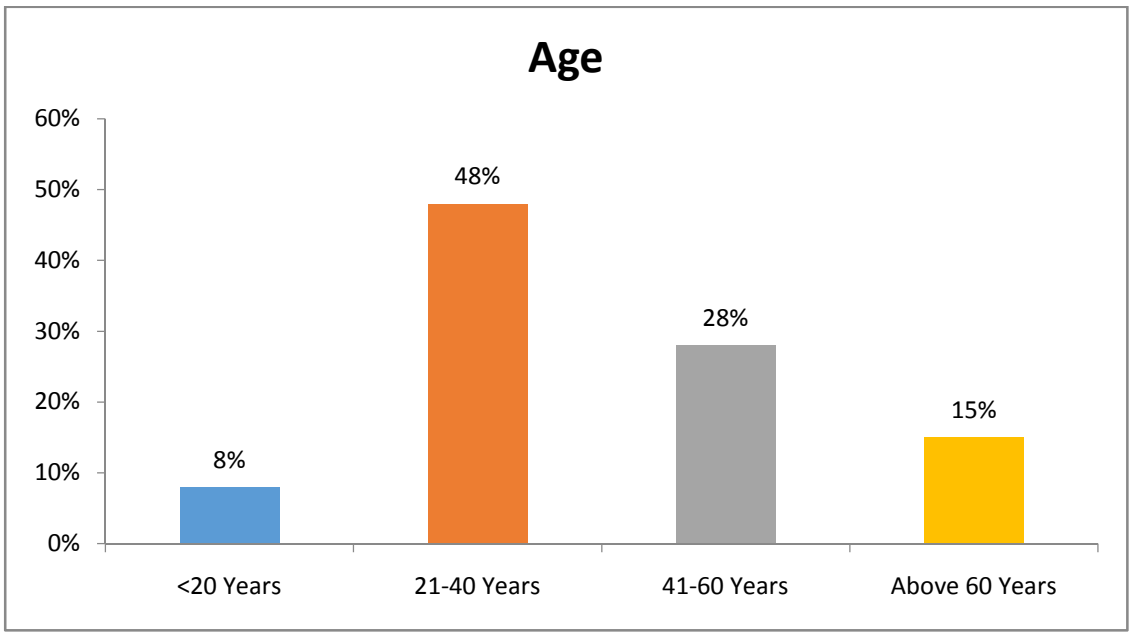
Presence of myopathy will be assessed by the values of serum CK, LDH, SGOT and correlated with fT_3, fT_4, TSH values. EMG and Muscle biopsy also done and correlated with fT_3, fT_4 and TSH. All the data obtained were entered in the proforma (enclosed).Data were analysed using SPSS package, and by chi-square tests, independency tests.

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

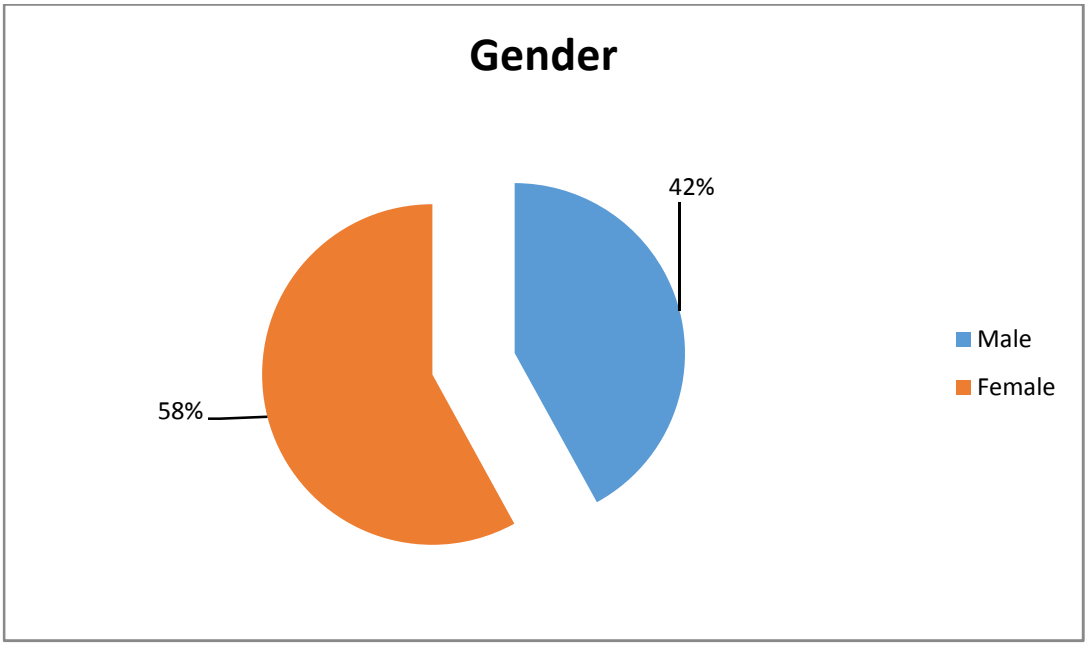
AGE DISTRIBUTION

age score	Frequency	Percent
<20 Years	4	8.0
21-40 Years	24	48.0
41-60 Years	14	28.0
Above 60 Years	8	16.0
Total	50	100.0



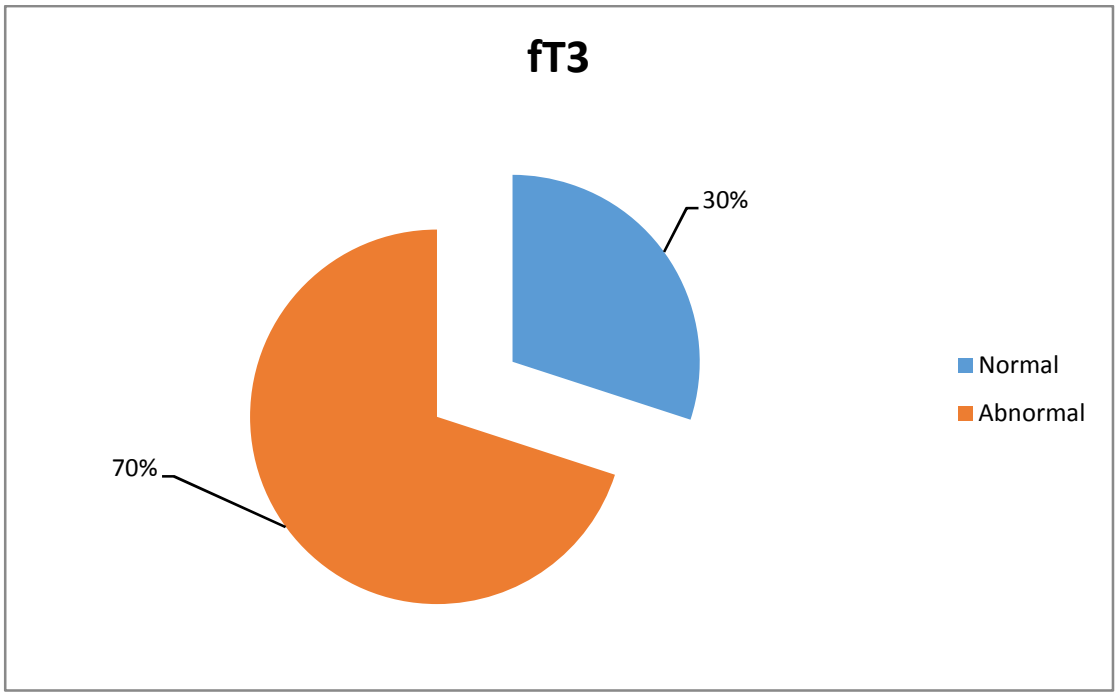
GENDER DISTRIBUTION

Gender	Frequency	Percent
Male	21	42.0
Female	29	58.0
Total	50	100.0



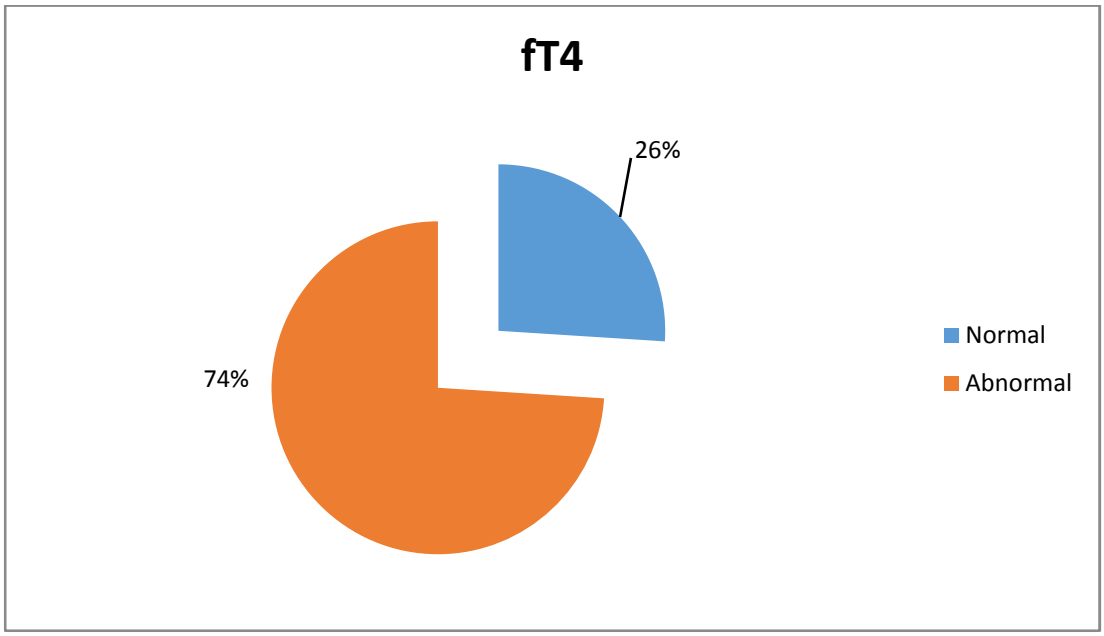
fT_3 SCORE

fT3	Frequency	Percent
Normal	15	30.0
Abnormal	35	70.0
Total	50	100.0



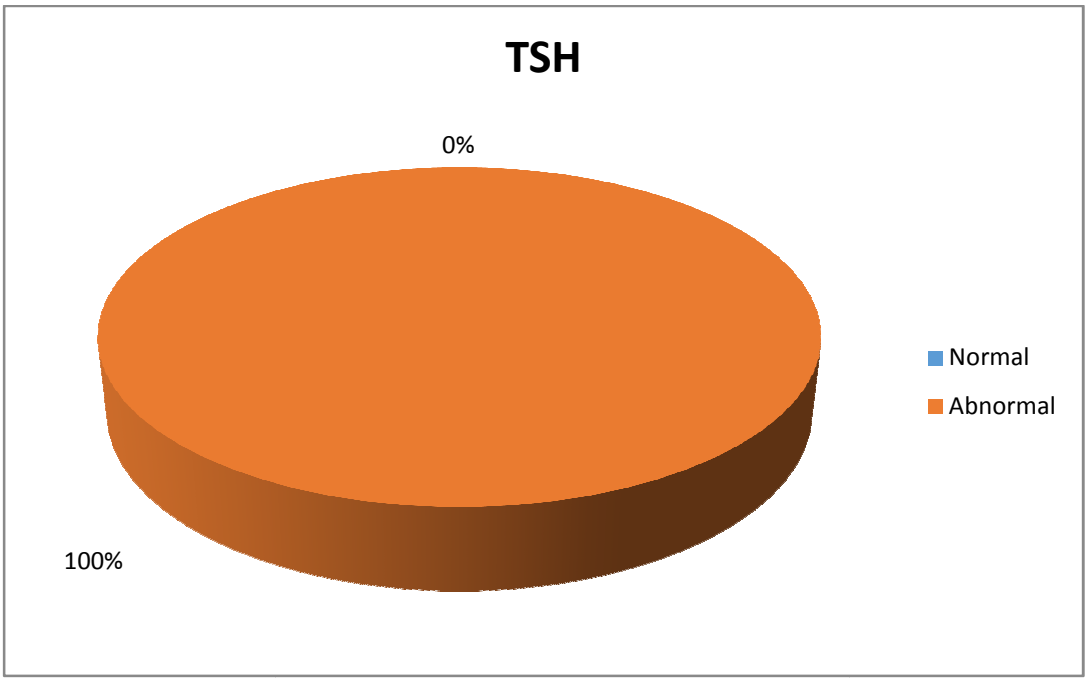
fT_4 SCORE

fT4	Frequency	Percent
Normal	13	26.0
Abnormal	37	74.0
Total	50	100.0



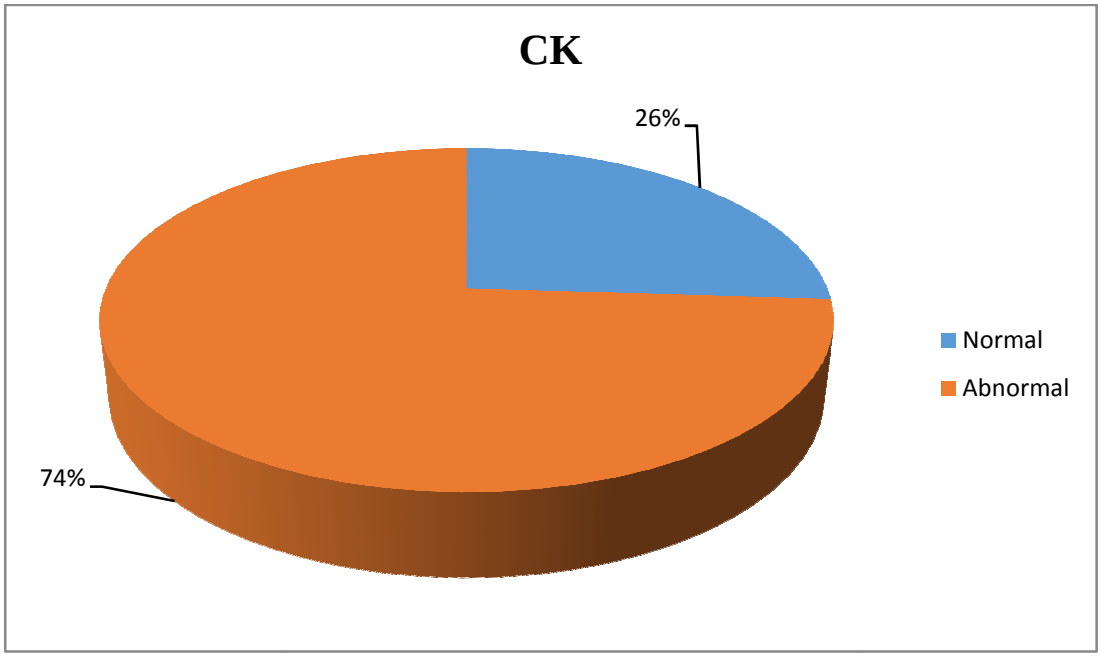
TSH SCORE

TSH	Frequency	Percent
Normal	0	00.0
Abnormal	50	100.0
Total	50	100.0



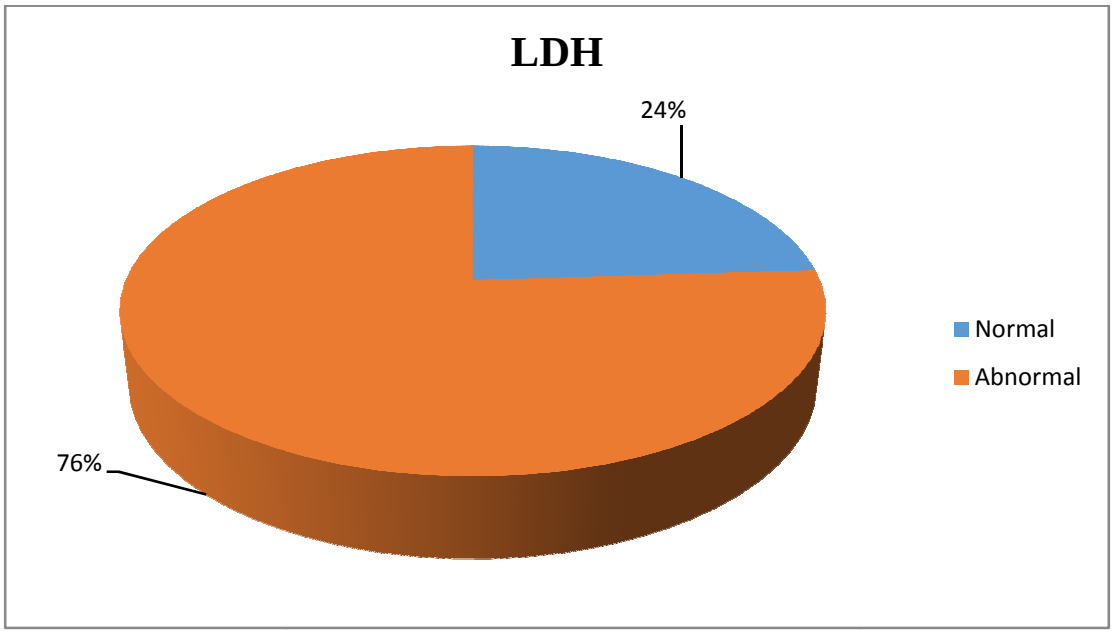
CK SCORE

CK	Frequency	Percent
Normal	13	26.0
Abnormal	37	74.0
Total	50	100.0



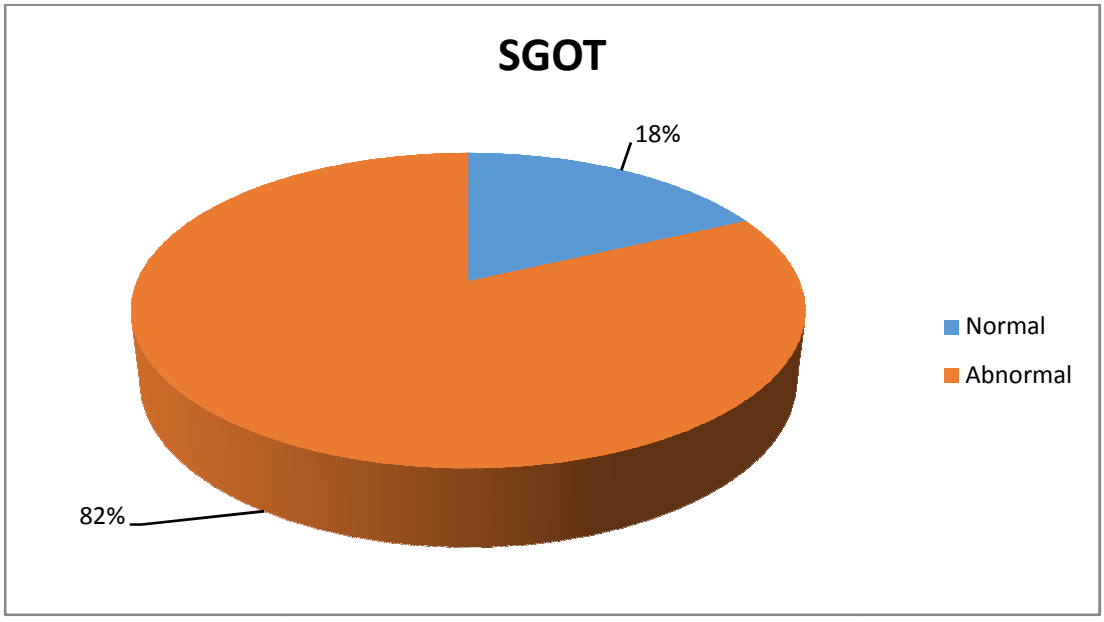
LDH SCORE

LDH	Frequency	Percent
Normal	12	24.0
Abnormal	38	76.0
Total	50	100.0



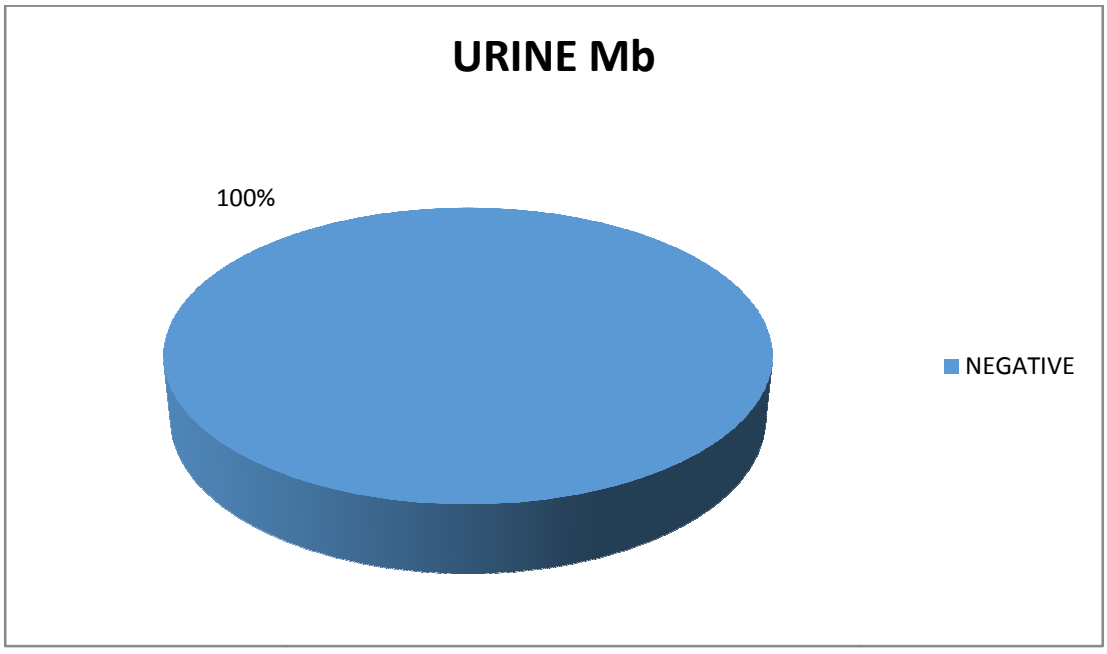
SGOT SCORE

SGOT	Frequency	Percent
Normal	9	18.0
Abnormal	41	82.0
Total	50	100.0



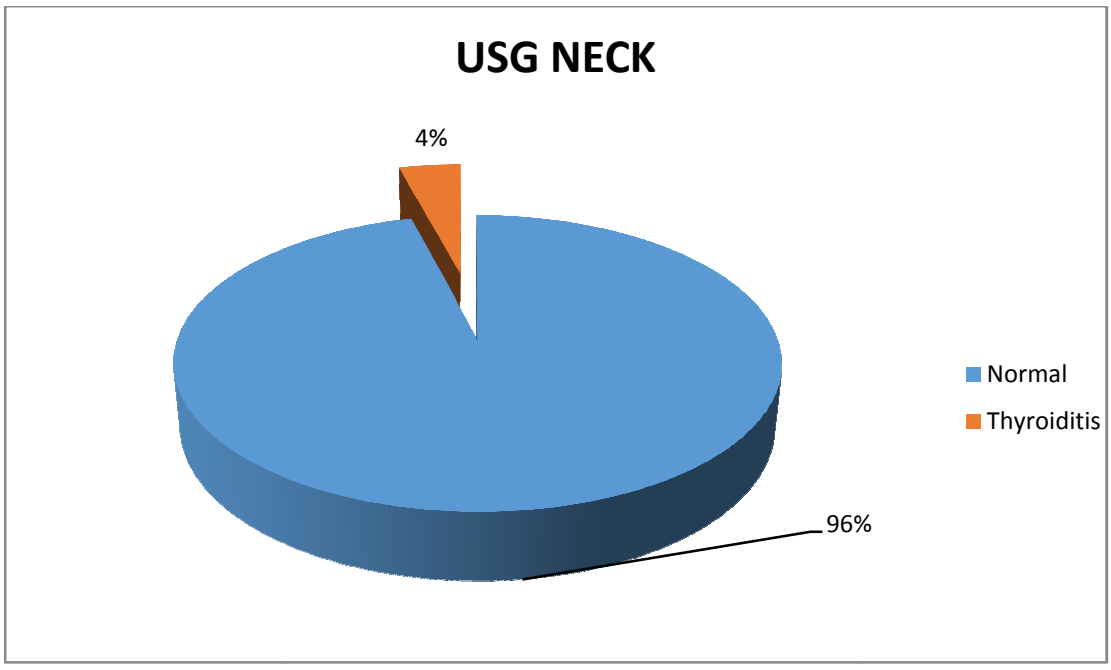
URINE MYOGLOBIN

URINE Mb	Frequency	Percent
Negative	50	100.0
Positive	0	0.0
Total	50	100.0



USG-NECK

USG Neck	Frequency	Percent
Normal	48	96.0
Thyroiditis	2	4.0
Total	50	100.0



EMG

EMG		Frequency	Percent
Valid		45	90.0
	Positive	5	10.0
	Total	50	100.0

MUSCLE BIOPSY

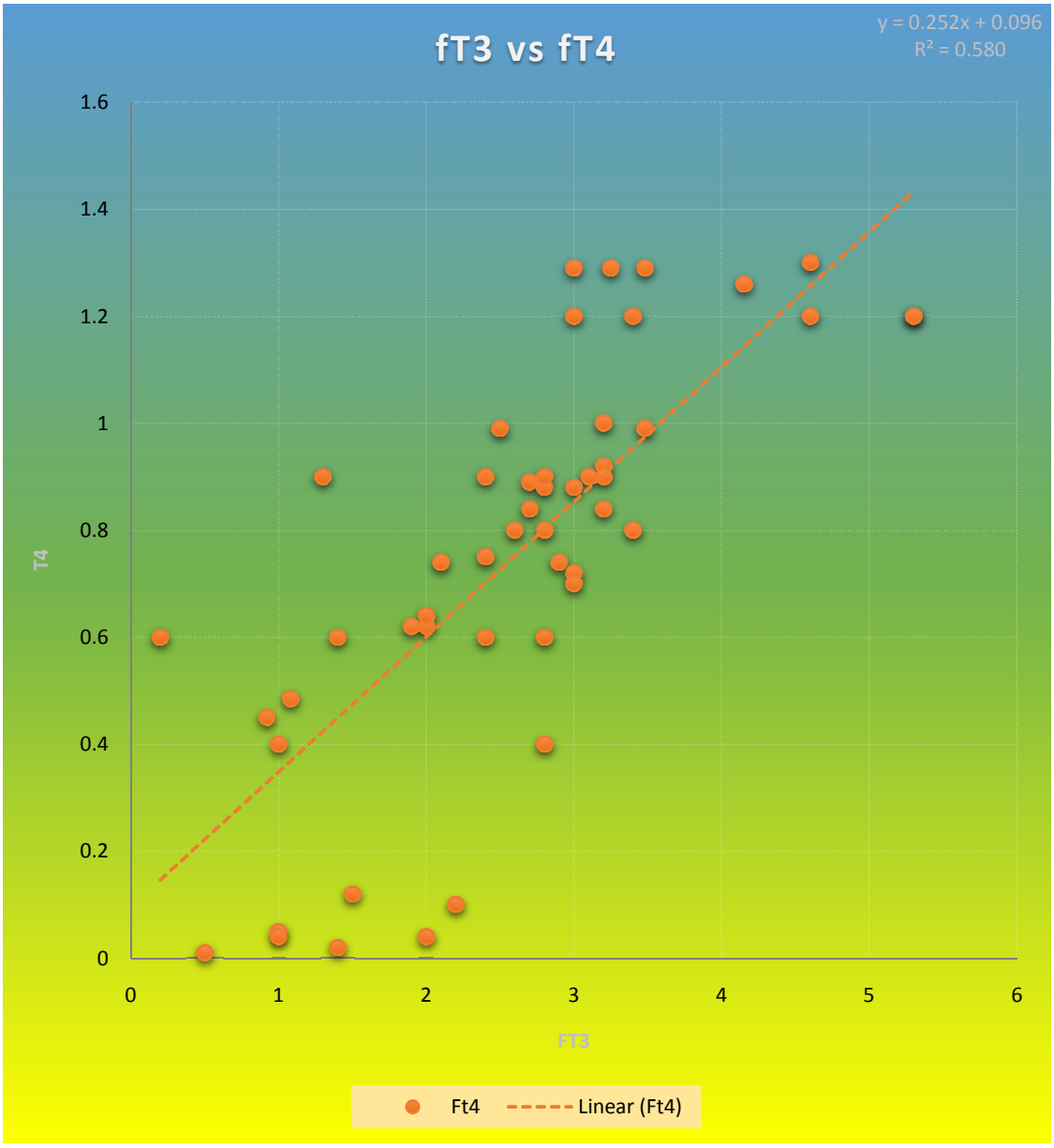
Muscle Biopsy		Frequency	Percent
Valid		45	90.0
	Positive	5	10.0
	Total	50	100.0

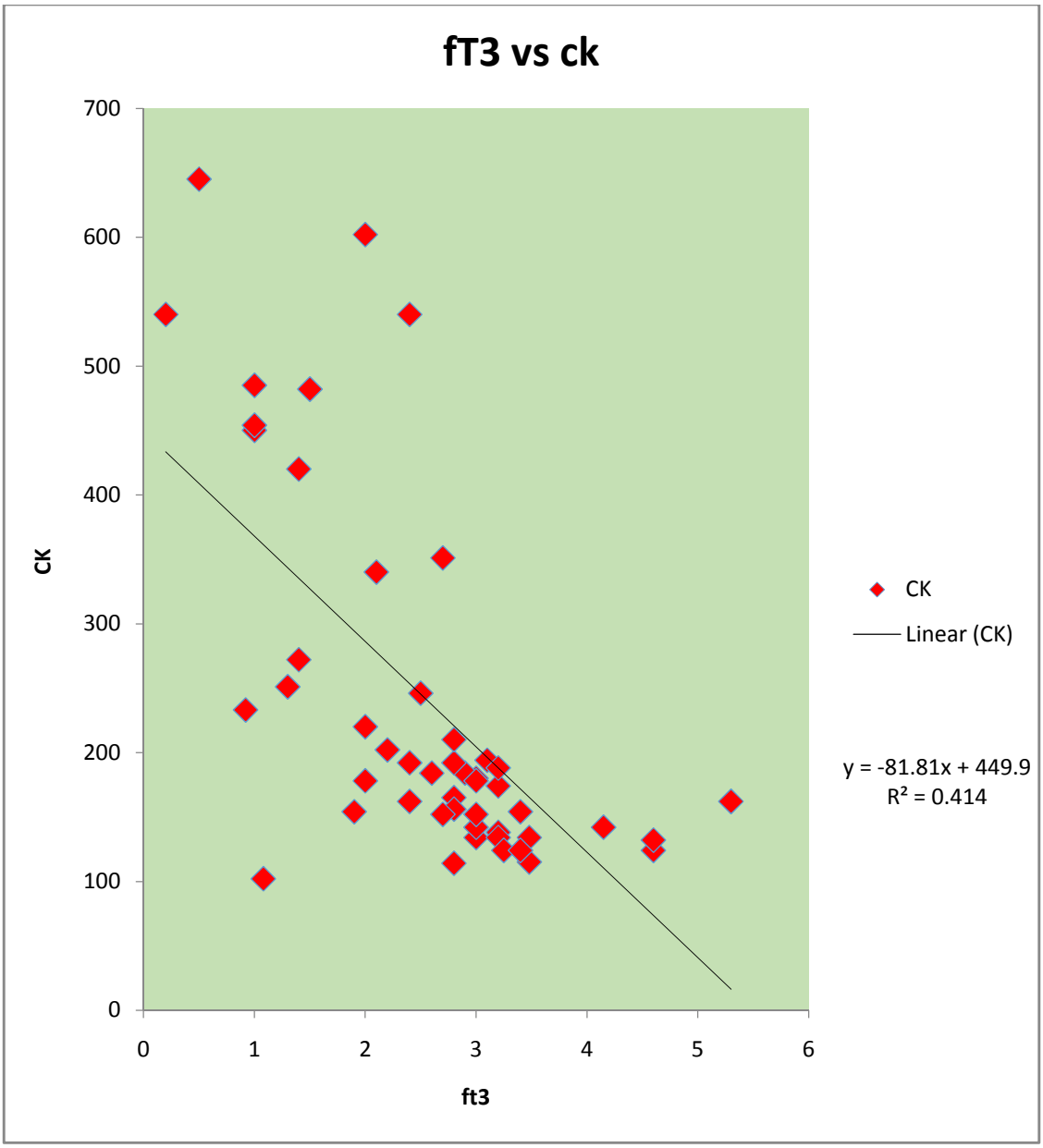
GROUP STATISTICS

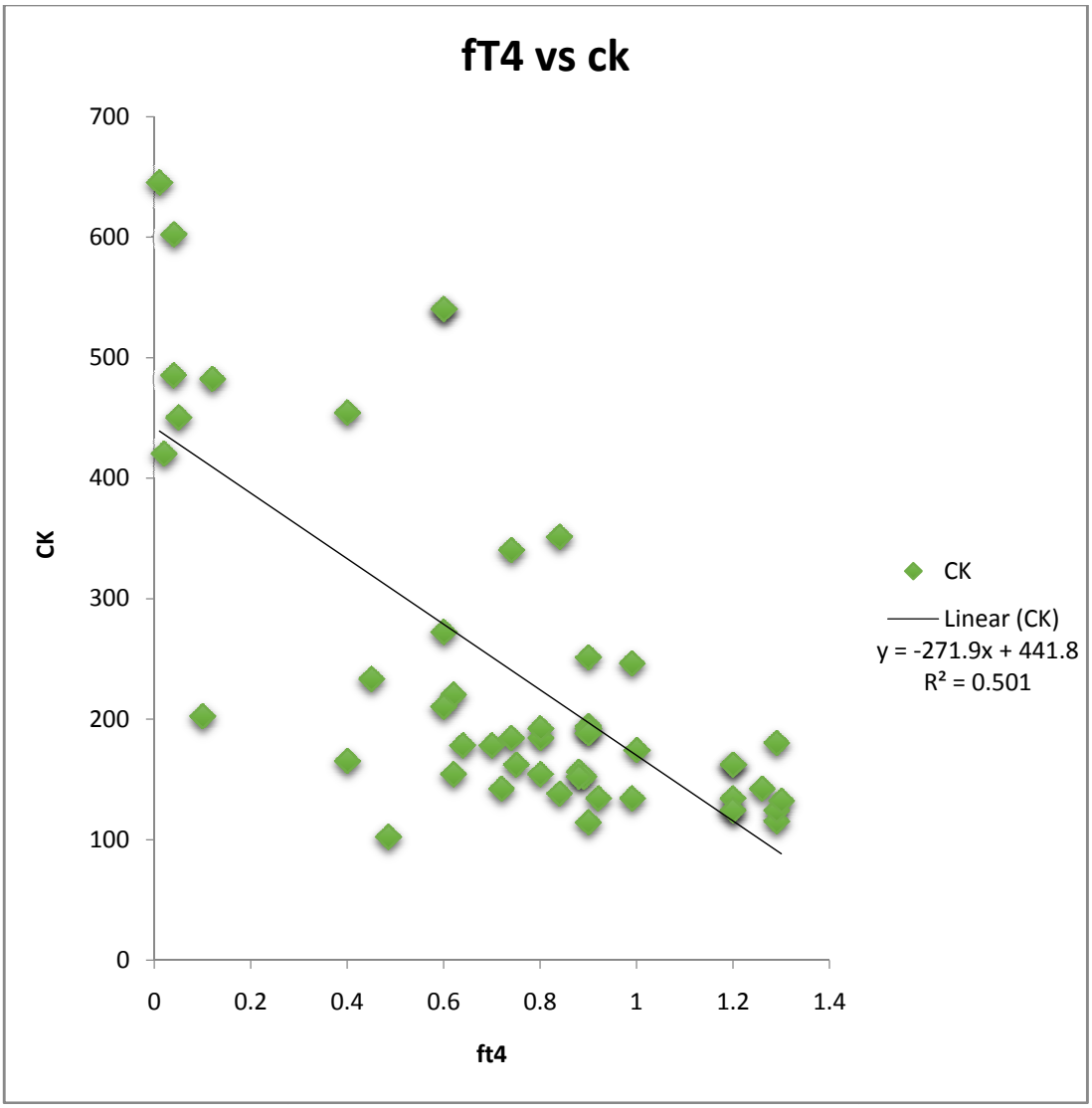
Group Statistics						
	SEX	N	Mean	Std. Deviation	Std. Error Mean	t value
Ft3	Male	21	2.6062	1.23029	.26847	0.037NS
	Female	29	2.5941	1.06289	.19737	
Ft4	Male	21	.7607	.34143	.07451	0.138 NS
	Female	29	.7459	.39886	.07407	
TSH	Male	21	39.4962	50.55331	11.03164	0.395 NS
	Female	29	45.2276	50.80502	9.43426	
CK	Male	21	237.2857	152.64834	33.31060	0.001 NS
	Female	29	237.3103	138.13919	25.65180	
LDH	Male	21	323.9048	158.74757	34.64156	0.326 NS
	Female	29	310.5862	129.48952	24.04560	
SGOT	Male	21	71.0571	45.84265	10.00369	0.164 NS
	Female	29	72.9310	34.99279	6.49800	

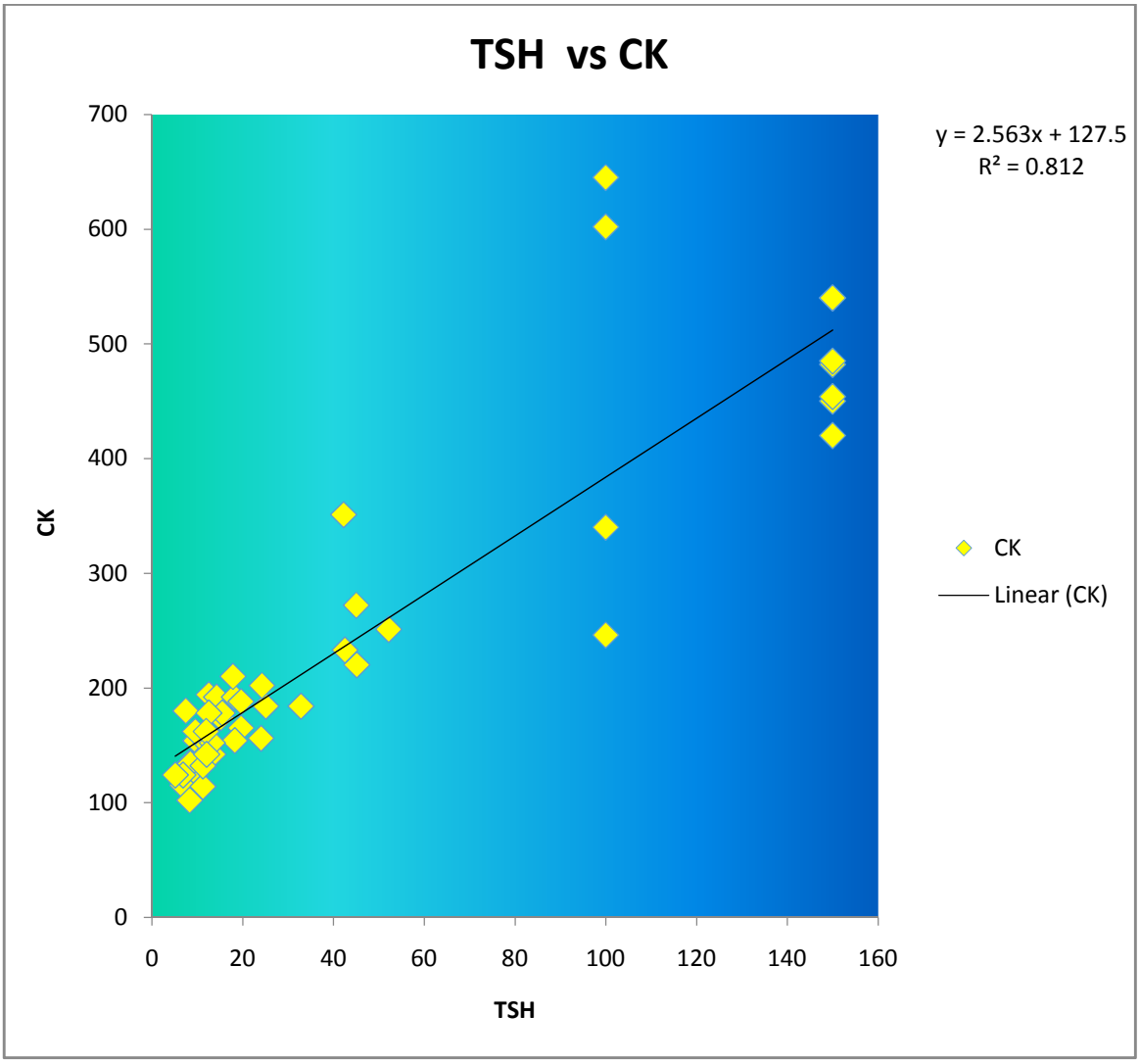
CORRELATIONS

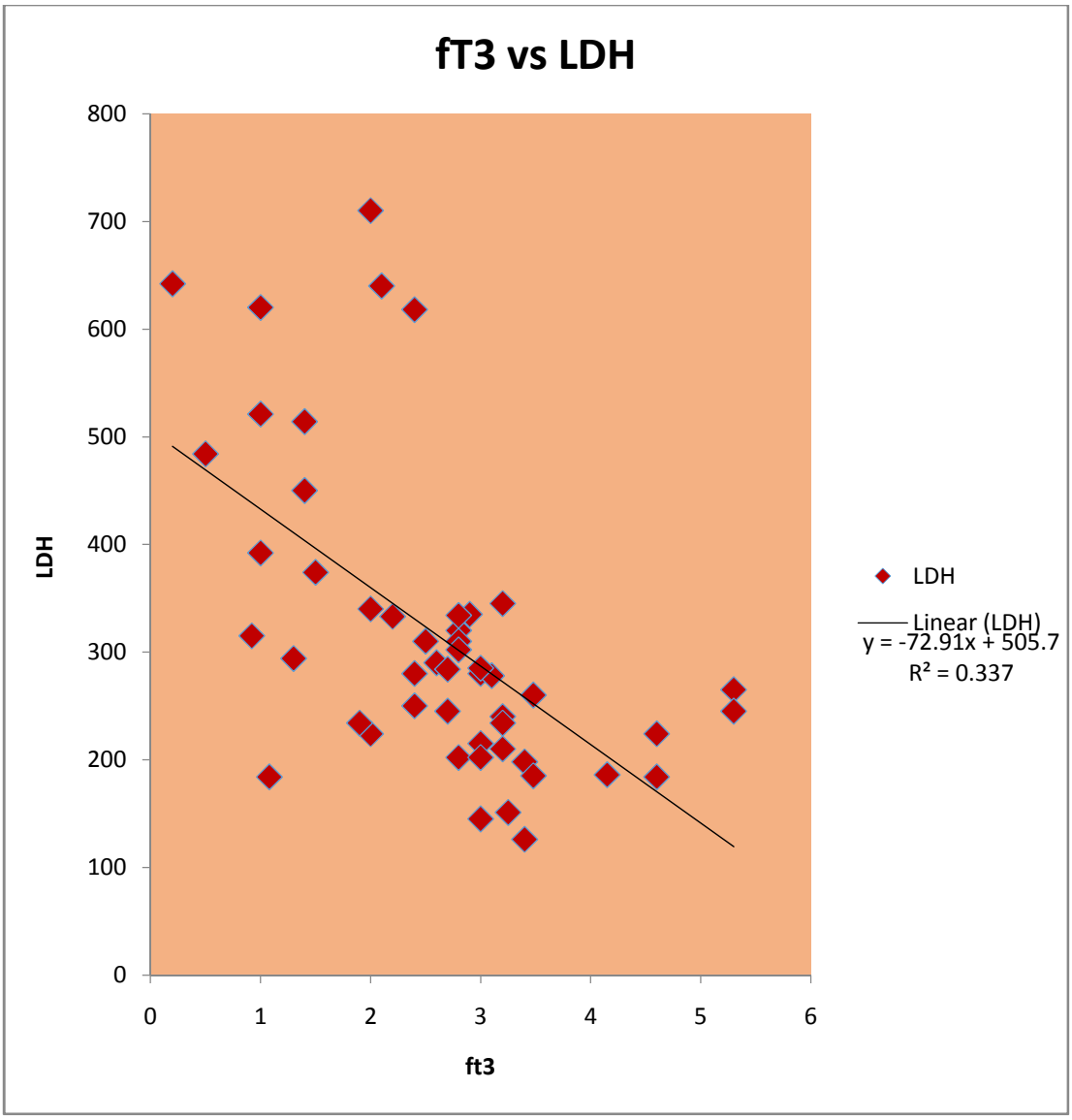
Correlations							
		Ft3	Ft4	TSH	CK	LDH	SGOT
Ft3	Pearson Correlation		.762**	-.653**	-.644**	-.581**	-.587**
Ft4	Pearson Correlation	.762**		-.671**	-.708**	-.627**	-.614**
TSH	Pearson Correlation	-.653**	-.671**		.902**	.821**	.782**
CK	Pearson Correlation	-.644**	-.708**	.902**		.839**	.836**
LDH	Pearson Correlation	-.581**	-.627**	.821**	.839**		.855**
SGOT	Pearson Correlation	-.587**	-.614**	.782**	.836**	.855**	
**. Correlation is significant at the p<0.01 level							

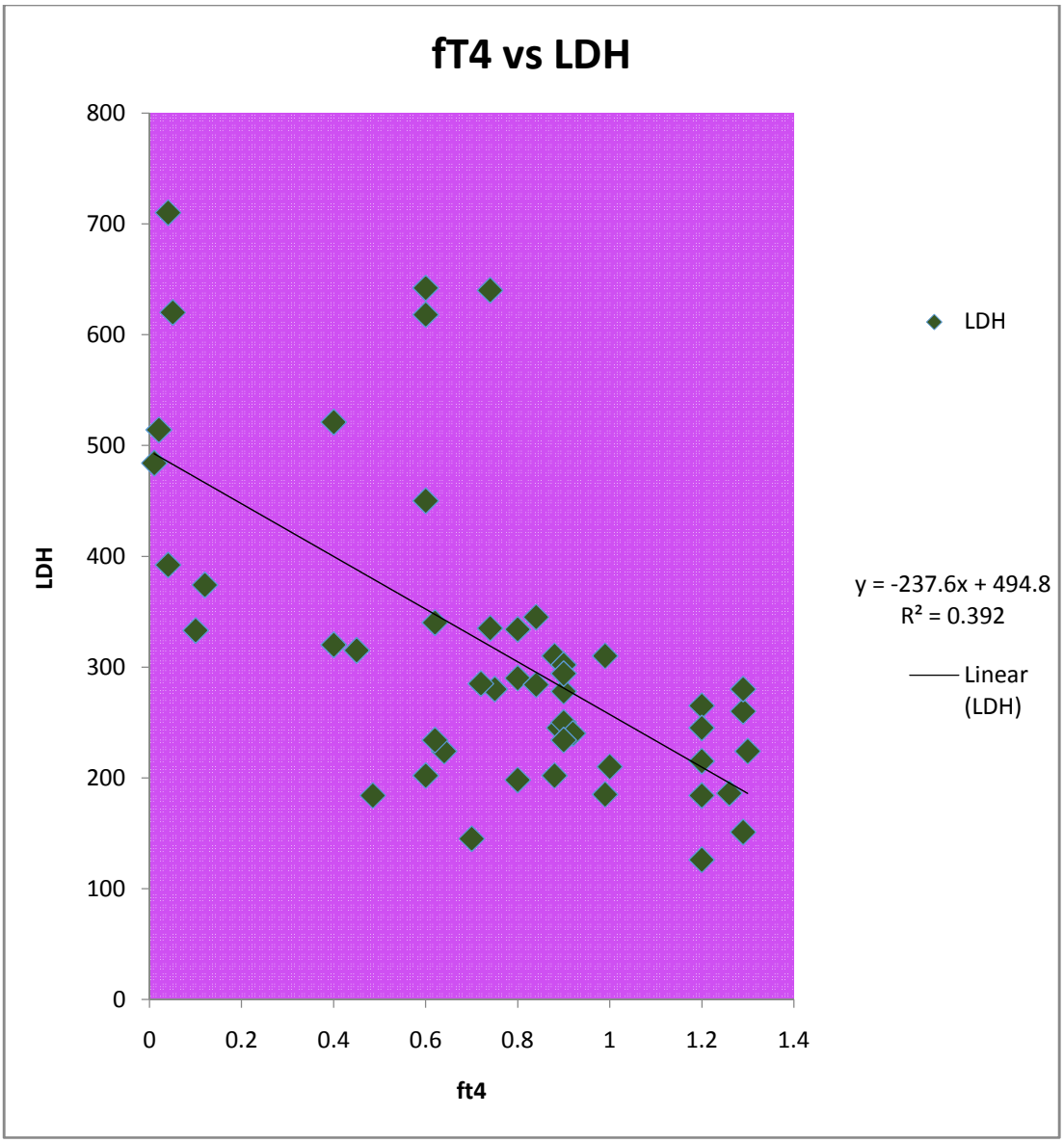

fT3 vs fT4
y = 0.252x + 0.096
R² = 0.580
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
FT4
0
1
2
3
4
5
6
FT3
Ft4
Linear (Ft4)

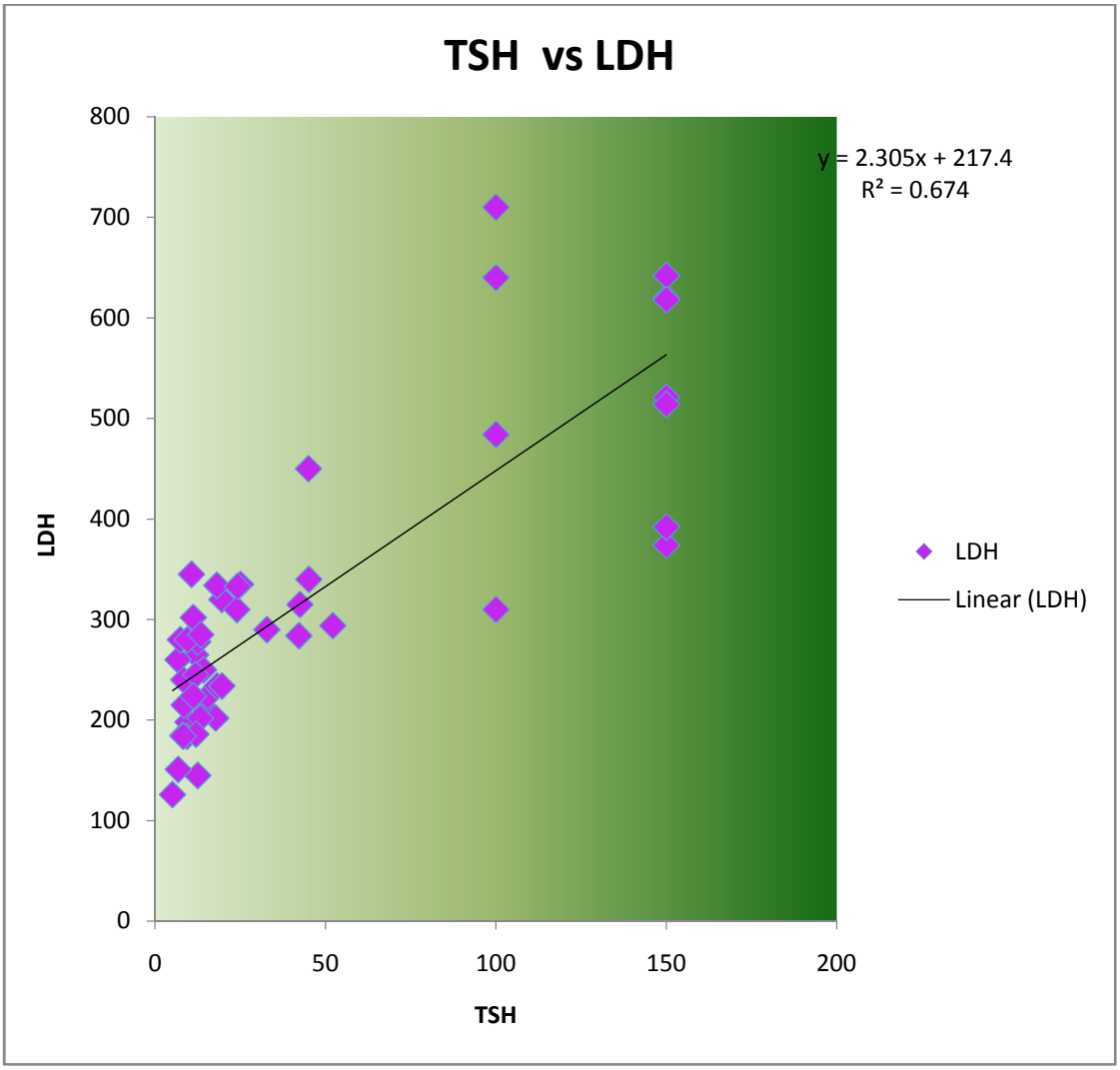

fT3 vs ck
700
600
500
400
300
200
100
0
CK
0
1
2
3
4
5
6
ft3
CK
Linear (CK)
y = -81.81x + 449.9
R² = 0.414


fT4 vs ck
700
600
500
400
300
200
100
0
CK
0
0.2
0.4
0.6
0.8
1
1.2
1.4
ft4
CK
Linear (CK)
y = -271.9x + 441.8
R² = 0.501


TSH vs CK
y = 2.563x + 127.5
R² = 0.812
CK
Linear (CK)
CK
TSH
0
100
200
300
400
500
600
700
0
20
40
60
80
100
120
140
160


fT3 vs LDH
800
700
600
500
400
300
200
100
0
LDH
0
1
2
3
4
5
6
ft3
LDH
Linear (LDH)
y = -72.91x + 505.7
R² = 0.337


fT4 vs LDH
800
700
600
500
400
300
200
100
0
LDH
0
0.2
0.4
0.6
0.8
1
1.2
1.4
ft4
LDH
y = -237.6x + 494.8
R² = 0.392
Linear (LDH)


TSH vs LDH
y = 2.305x + 217.4
R² = 0.674
LDH
Linear (LDH)
LDH
TSH
800
700
600
500
400
300
200
100
0
0
50
100
150
200

DESCRIPTIVE STATISTICS

	Mean	95% Confidence Interval for Mean		Median	Std. Deviation	Minimum	Maximum
		Lower Bound	Upper Bound				
AGE	39.78	35.65	43.91	39.00	14.54	17.00	65.00
Ft3	2.60	2.28	2.92	2.80	1.12	0.20	5.30
Ft4	0.75	0.65	0.86	0.80	0.37	0.01	1.30
TSH	42.82	28.54	57.10	16.63	50.26	4.70	150.00
CK	237.30	196.69	277.91	179.00	142.88	102.00	645.00
LDH	316.18	276.08	356.28	282.00	141.11	126.00	710.00
SGOT	72.14	60.93	83.36	66.00	39.48	6.20	162.00

RESULTS

AGE DISTRIBUTION

In our study mean age group is 39.78 years. About 48% of patients Are between 21-40 years, About 28% of patients are between 41-60 years. About 8% and 16% are above 60 and below 20 years respectively.

GENDER DISTRIBUTION

In our study 58% are females and 42% are males.

fT_3 DISTRIBUTION

In our study, 30% have normal T_3 and 70% have abnormal T_4.

fT_4 DISTRIBUTION

In our study 26% have normal T_3 and 74% have abnormal T_4.

SERUM TSH DISTRIBUTION

In our study, 100% have abnormal TSH.

SERUM CK DISTRIBUTION

In our study 24% have normal CK and 74% have abnormal CK.

SERUM LDH DISTRIBUTION

In our study, 26% have normal LDH and 74% have abnormal LDH

SERUM SGOT DISTRIBUTION

In our study 18% have normal SGOT and 82% have abnormal SGOT.

URINE MYOGLOBIN DISTRIBUTION

In our study 100% have negative myoglobin.

USG-NECK DISTRIBUTION

In our study, 96% have normal USG- Neck and 4% have thyroiditis.

EMG DISTRIBUTION

In our study, EMG was done in 5 patients who have given consent and the results were positive for all 5 patients.

MUSCLE BIOPSY DISTRIBUTION

In our study, Muscle biopsy was done in 5 patients who have given consent and the results were positive for all 5 patients.

DISCUSSION

DISCUSSION

In this study 50 patients with hypothyroidism admitted in RGGGH and attending Endocrine OP, Chennai, based on inclusion, exclusion criteria were analyzed. They were subjected to detailed clinical examination and presence of skeletal myopathy in hypothyroidism patients were analyzed. Serum TFT, fT3, fT4, CK, LDH, SGOT, urine myoglobin, USG-neck, EMG. Serum TFT is correlated with serum CK, LDH, SGOT, EMG, Muscle biopsy and p value obtained was statistically significant indicating significant association between them.

AGE

In our study mean age is 39.78 years, standard deviation is 14.54, median is 39.

GENDER

In our study 58% are females and 42% are males. In gender distribution p value is not significant. (>0.05)

CORRELATION OF fT_3 WITH fT_4 , TSH, CK, LDH, SGOT

In our study fT_3 shows positive correlation with fT_4 and negative correlation with TSH,CK,LDH,SGOT, has a significant p value of<0.01.

CORRELATION OF fT_4 WITH fT_3, TSH, CK, LDH, SGOT

In our study fT_4 shows positive correlation with fT_3 and negative correlation with TSH, CK, LDH, SGOT, has a significant p value of <0.01.

CORRELATION OF TSH WITH fT_3, fT_4, CK, LDH, SGOT

In our study TSH shows negative correlation with fT_3,fT_4 and positive correlation with CK, LDH and SGOT, has a significant p value of <0.01.

CORRELATION OF TSH WITH EMG & MUSCLE BIOPSY

In our study, 5 patients who gave consent are subjected for EMG and muscle biopsy, in whom TSH>100.TSH shows positive correlation with EMG and muscle biopsy.EMG showed polyphasic action potentials / hyperirritability. Muscle Biopsy-muscles are pale and swollen. Muscle fibres - swollen, striations are lost, and separated by mucinous deposits. Type 1 muscle fibres predominate.

CONCLUSION

CONCLUSION

This study shows high CK, LDH and SGOT in hypothyroid patients with clinical features suggesting myopathy. EMG and Muscle biopsy were positive. This showed presence and severity of myopathy in hypothyroid patients. As hypothyroid myopathy is reversible with eltroxin treatment, hypothyroidism should be ruled out in every patient presenting with myopathy. Myopathy in hypothyroidism can be identified by serum CK, LDH, and SGOT. Myopathy in hypothyroidism has good prognosis, if properly treated with thyroxine.

LIMITATIONS

LIMITATIONS

- Sample size is small, this study should be conducted in large number of patients.
- As EMG and MUSCLE BIOPSY are invasive, they can be done only in patients who are giving consent.

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BIBLIOGRAPHY

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ANNEXURES

PROFORMA

CLINICAL & BIOCHEMICAL CORRELATION OF SKELETAL MYOPATHY IN HYPOTHYROID PATIENTS

Name :

Age :

Sex :

IP Number :

Address :

Occupation :

Socioeconomic status :

Presenting Complaints:

- Muscle Weakness
- Cramps
- Stiffness
- Muscle Swelling

Past History:

- Thyroid disorders
- Type 2 Diabetes Mellitus
- SHTN
- CAD
- CVA
- CKD

Family History :

Treatment History :

General Examination:

- Conscious
- Oriented
- Afebrile
- Icterus
- Clubbing
- Cyanosis
- Pedal edema
- Generalized lymphadenopathy
- Neck swelling
- Eye signs
- Any hypertrophy of calf muscle

Vital Signs

- Pulse rate
- Blood Pressure
- Respiratory rate

Systemic Examination

- RS
- CVS
- P/A
- CNS – Deep Tendon reflexes

Investigations:

Serum CK	
Serum LDH	
Serum SGOT	
Serum TFT	
Urine Mb	
USG – Neck	
EMG	
Muscle Biopsy	

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telcphone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.G.Divya Prabha
Post Graduate in M.D.(General Medicine)
Institute of Internal Medicine
Madras Medical College
Chennai 600 003

Dear Dr.G.Divya Prabha,

The Institutional Ethics Committee has considered your request and approved your study titled **"CLINICAL & BIO-CHEMICAL CORRELATION OF SKELETAL MYOPATHY IN HYPOTHYROID PATIENTS " - NO.22022017**

The following members of Ethics Committee were present in the meeting hold on **07.02.2017** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.M.K.Muralidharan,MS.,M.Ch.,Dean, MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.S.Suresh, MS., Prof.of Surgery, MMC, Ch-3	: Member
5.Prof.Baby Vasumathi,MD.,Director, Inst. of O & G	: Member
6.Prof.K.Ramadevi,MD.,Director,Inst.of Bio-Che,MMC,Ch-3	: Member
7.Prof.R.Padmavathy, MD, Director,Inst.of Pathology,MMC,Ch-3	: Member
8.Prof.S.Mayilvahanan,MD,Director, Inst. of Int.Med,MMC, Ch-3	: Member
9.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
10.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
11.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

URKUND

Urkund Analysis Result

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CERTIFICATE - II

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Guide & Supervisor sign with Seal.

INFORMATION SHEET

We are conducting a study on **"Clinical & Biochemical Correlation of Skeletal Myopathy in Hypothyroid Patients"** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your co-operation to undergo relevant investigations as per need may be valuable to us.

The purpose of this study is to find the myopathy in hypothyroidism and prevent it at the earliest.

We are selecting certain cases and if you are found eligible, we would like to perform extra tests and you will be subjected to a blood investigation, which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Date :
Place :

Signature of Investigator

Signature/left thumb impression of Participant

PATIENT CONSENT FORM

Study Detail : **"CLINICAL & BIOCHEMICAL CORRELATION OF SKELETAL MYOPATHY IN HYPOTHYROID PATIENTS"**

Study Centre : Rajiv Gandhi Government General Hospital, Chennai.

Patient's Name :

Patient's Age :

In Patient Number :

Patient may check (√) these circles

a) I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. o

b) I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. o

c) I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. o

d) I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. o

e) I hereby consent to participate in this study. o

f) I hereby give permission to undergo detailed clinical examination and relevant investigations as required. o

Signature/thumb impression

Patient's Name and Address:

Signature of Investigator

Study Investigator's Name:

Dr.G.DIVYA PRABHA

MASTER CHART

SI.NO	AGE	SEX	Ft3	Ft4	TSH	CK	LDH	SGOT	Urine Mb	USG-Neck	EMG	Muscle Biopsy
			(3.1-6.8pmol/L)	(0.93-1.7ng/dl)	(0.5-5IU/L)	(35-145U/L)	(125-220U/L)	(5-35IU/L)				
1	40	F	2	0.62	45.12	220	340	84	Negative	Normal		
2	26	F	3.4	0.8	9.6	154	198	40	Negative	Normal		
3	23	F	3.2	1	15.12	174	210	55	Negative	Normal		
4	65	M	5.3	1.2	11.9	162	265	24	Negative	Normal		
5	27	F	4.6	1.2	9.4	124	184	44	Negative	Normal		
6	26	F	3.48	1.29	6.7	115	260	72	Negative	Normal		
7	54	F	2.1	0.74	100	340	640	124	Negative	Normal	Positive	Positive
8	32	M	3	1.29	7.4	180	280	62	Negative	Normal		
9	34	F	3.48	0.99	8.2	134	185	45	Negative	Normal		
10	63	F	2.8	0.4	19.6	165	320	82	Negative	Normal		
11	56	F	2.6	0.8	32.8	184	290	62	Negative	Normal		
12	47	M	3.1	0.9	12.5	194	278	70	Negative	Normal		
13	52	F	1.4	0.6	45	272	450	94	Negative	Normal		
14	34	F	1	0.05	>150	450	620	124	Negative	Normal	Positive	Positive
15	42	M	2.8	0.88	24	156	310	90	Negative	Normal		
16	47	M	0.2	0.6	>150	540	642	152	Negative	Normal	Positive	Positive
17	27	F	2.9	0.74	25.06	184	335	98	Negative	Normal		
18	65	M	3.2	0.84	10.69	138	345	81	Negative	Normal		
19	63	F	0.5	0.01	>100	645	484	146	Negative	Normal	Positive	Positive
20	26	F	3	1.2	8.5	134	215	76	Negative	Normal		
21	48	M	2.7	0.89	11.91	152	245	62	Negative	Normal		
22	20	F	2.4	0.9	14.2	192	250	80	Negative	Normal		
23	27	M	1	0.4	>150	454	521	151	Negative	Thyroiditis		
24	26	F	2.8	0.8	18.1	192	334	102	Negative	Normal		
25	38	F	2.4	0.75	9.5	162	280	42	Negative	Normal		

26	40	M	2	0.64	15.46	178	224	71	Negative	Normal		
27	40	M	2	0.04	>100	602	710	162	Negative	Normal		
28	29	F	2.7	0.84	42.2	351	284	72	Negative	Normal		
29	18	F	2.8	0.9	11.2	114	302	24	Negative	Normal		
30	38	M	3	0.72	13.4	142	285	42	Negative	Normal		
31	47	F	1.4	0.02	>150	420	514	92	Negative	Thyroiditis		
32	60	M	2.2	0.1	24.2	202	333	62	Negative	Normal		
33	22	F	3.2	0.92	8.4	134	240	32	Negative	Normal		
34	34	M	2.8	0.6	17.8	210	202	42	Negative	Normal		
35	17	F	3	0.7	12.5	178	145	28	Negative	Normal		
36	42	M	1.9	0.62	18.2	154	234	52	Negative	Normal		
37	62	F	1.5	0.12	>150	482	374	114	Negative	Normal	Positive	Positive
38	37	M	1.3	0.9	52.14	251	294	6.2	Negative	Normal		
39	62	M	3	0.88	13.26	152	202	41	Negative	Normal		
40	47	F	0.92	0.45	42.5	233	315	89	Negative	Normal		
41	61	M	3.25	1.29	6.8	124	151	32	Negative	Normal		
42	63	F	1	0.04	>150	485	392	128	Negative	Normal		
43	28	M	5.3	1.2	11.9	162	245	52	Negative	Normal		
44	33	F	2.5	0.99	>100	246	310	78	Negative	Normal		
45	21	M	3.2	0.9	19.6	188	234	62	Negative	Normal		
46	18	F	4.6	1.3	11.2	132	224	18	Negative	Normal		
47	29	M	2.4	0.6	>150	540	618	152	Negative	Normal		
48	42	F	3.4	1.2	4.7	124	120	28	Negative	Normal		
49	46	F	4.15	1.26	12	142	186	42	Negative	Normal		
50	45	M	1.08	4.85	8.26	102	184	24	Negative	Normal		